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VOLUME IV

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CHAPTER LXII

DISEASES OF THE PLEURA

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PRINCIPLES OF PHYSICS IN PLEURAL CONDITIONS

Because of the essential rôle of differential pressures in external and internal respiration, a brief resumé of the physical principles involved is essential to a better understanding of the diseases of the pleuræ and lungs. It is only indirectly, however, that pleural disease has to do with internal respiration and that dependent upon the associated or resultant injury to lung tissue proper and there will here be considered mainly the physics of external respiration.

Intrapleural Tension.[33]—Due to the increased growth of the osseocartilaginous thorax proportionate to the growth of the lungs[17] and the inherent elasticity of the lungs, there is present in the intrapleural cavity a pressure less than atmosphere which is referred to as intrapleural tension. Intrapleural tension approximately equals the elastic strain of the lungs, though it varies also as the rigidity of the osseocartilaginous cage and the respiratory movement. The lessened rigidity of the thorax in children renders the respiratory factor and elastic strain less potent to create a negative pressure.

Normal intrapleural tension varies between 6 and 8 mm. Hg at the beginning of inspiration and 4 and 5 mm. at the beginning of expiration, the lesser negative pressure in the latter case being due to the overcoming of the elasticity by the distention of the alveoli with air. Normally intrapleural tension never equals atmospheric pressure but with open or valvular pneumothorax may reach atmospheric and even become positive. On exertion, the negativity may go as high as 100 mm. Hg.

When intrapleural tension becomes atmospheric pressure or positive, due to introduction of air, the elasticity of the lungs manifests itself in one direction and the lungs collapse unless bound by adhesions. This latter factor stays the collapse and thus it is that the paradoxical clinical observation that pneumothorax in the healthy lung causes greater distress than in the diseased lung is explained. Upon collapse of one lung a complementary hypertrophy and increased elasticity of the opposite lung occurs. To this the name complementary emphysema has been erroneously applied for in emphysema the opposite condition of loss of elasticity prevails.

How much the elasticity of the lung is due to muscle fibers and how much to other factors, has not been determined. The tympanitic quality (Skodaic) of the note found over lung areas surrounding inflammatory zones and in many general disturbances without pulmonary lesions suggests a loss of muscular tonus as a factor. The frequency of tympanites in pneumonia and the finding of the Skodaic note suggest a decreased muscular tonus as an explanation of both.

The intrapleural space may be encroached upon by gas or fluid or both. The resultant effect of these is different chiefly due, in the case of serous effusions, to purely physical properties, i.e., greater density of fluids and tendency therefore to gravitate. With purulent fluids the problem is complicated by the pathological changes, i.e., adhesions and encapsulations.

Intrapleural Tension in Pneumothorax.[7]—Air may be present in the intrapleural space from a variety of sources. It may be introduced (1) *from without* through the chest wall, due to trauma or more frequently after paracentesis or exploratory puncture,[31] the incidence of which is extremely high according to *x*-ray plates. In punctured wounds one frequently encounters a subcutaneous emphysema and no evidence of pneumothorax, where, due to the negative pressure, theoretically the air would be expected to be present. The reason for this is not clear but West has suggested that the cohesion of the pleural layers[34] might be the explanation. It is to be remembered, however, that West did not have the advantages of *x*-ray pictures, and it is probable that small amounts of air in the intrapleural space can not be detected by ordinary methods of percussion and auscultation. (2) The air may enter *through ruptured pulmonary tissue* in which case the egress is always impeded and the ingress exceeds it. Here the expiratory intrapleural tension is above atmospheric pressure and lung compression follows. (3) The membranes may be intact and the air produced by an *anaërobic gas-producer.*[8, 14, 21] Here there will be no egress and the air must be absorbed, unless surgical measures are instituted. (4) Finally, the air may enter from below the diaphragm.

In any case one of three conditions may prevail. Either (1) *the egress may be greater than the ingress,* which is highly improbable, and would result in little alteration of pressure, except where the pneumothorax is closed and air is absorbing, pressure again is negative but the negativity is not as great as the negativity on the other side and the mediastinum may remain displaced. Or (2) *the egress may equal the ingress,* in which case collapse does not occur due to a further complicating factor, *the respiratory oscillation.* Pressure in the air tubes is not atmosphere, due to the resistance offered. The inspiratory pressure is negative on the average of 0.5 mm. Hg, and the expiratory pressure positive to 2 or 3 mm. Hg. This respiratory oscillation results therefore in a differential pressure sufficient to maintain the distention of the lungs even with intrapleural tension equal to atmospheric pressure. Furthermore, the differential gas pressure due to internal respiration in itself has been shown to be of more importance

than respiratory movement and would of itself account for a current. Finally, (3) *the ingress may exceed the egress* (valvular) where the expiratory pressure is positive and the lungs are compressed. The expiratory pressure is actually positive in most cases and the inspiratory never above atmospheric pressure unless fluid is present. The retention of a high positive pressure and its continuance suggest an extensive disease of the pleura because of failure of absorption.

The displaced intrathoracic viscera add further mechanical difficulties: (1) *Kinking of the great arterial trunks* or constriction of the inferior vena cava may add circulatory difficulties. (2) The collapsed lung not only decreases respiratory surfaces but offers *increased resistance to blood flow* in pulmonary capillaries so that the work of the right ventricle is increased, and (3) finally, *the collapsed and retracted lung may be sucked over* so as to encroach upon the functionating lung especially during inspiration when negativity is greatest and a vicious circle is established, for as the dyspnea increases, respiratory movement will become more violent, negativity will increase and the encroachment of the collapsed lung on the sound side will increase. How great a part this latter factor plays, has been demonstrated in artificial pneumothorax where stitching of the lung to the chest wall has abolished dyspnea where it previously existed.[4]

Intrapleural Tension in Serous Effusion.—Normally the pleural cavity contains a slight amount of fluid. Increase may occur by decreased lymph absorption or increased production in chemical composition varying in each case. The normal lymph current is from the vessels toward the root of the lung with some flow through diaphragm and chest wall. In inflammatory conditions which alone are here considered both increased production and decreased absorption are present. The intrapleural tension in such a case approaches atmospheric pressure and varies in different parts of the chest, being nearer atmospheric pressure in the dependent part. Why this difference in pressure should exist is not quite clear, but it explains the clinical observation of atelectasis above fluid. The lessened negativity is not in proportion to the amount of fluid, however. The respiratory oscillation here is small and usually absent. The removal of sufficient fluid to start respiratory oscillation initiates the lymph pump by the respiration motion and absorption follows.

Purulent Effusion.—The added factor of an actual high pressure of exudation further increases the intrapleural tension which may rise to +3 as high as +16 mm. Hg.

CHEMISTRY OF DISEASES OF THE PLEURÆ[15]

Normal pleural fluid is present in insufficient quantities for accurate chemical analysis, but must differ so little from transudate fluid which in turn is comparable to normal lymph that available analyses of transudate fluid may be accepted as figures for normal pleural fluid. The presence of the formed cellular elements and probably alteration

in capillary permeability account for the different compositions of exudates.

Physical Properties.—Normal or transudate fluid is usually a clear straw or yellow fluid of a specific gravity of 1010 to 1015. It coagulates slowly or not at all. The molecular concentration as determined by the freezing point equals that of serum. In tuberculosis and inflammatory fluids the freezing point is lowered from 0.56 degrees to 0.523 degrees of pleural fluid in the same individual. Exudate fluid may be clear or turbid and the color may vary as the invading organism. The specific gravity is over 1018 usually and spontaneous coagulation occurs.

Protein Content.—Transudates always contain the less viscous of the proteins, seralbumin and serglobulin and occasionally the more viscous fibrinogen. Proteoses and peptones are found only where autolysis has occurred. The protein content is between 10 and 30 p.p.m. of which 0.1 p.p.m. is fibrinogen. The protein percentage may be higher, however, in old fluids where resorption of water has occurred. Contrariwise the percentage may be low in exudates in hydremic states. Inflammatory fluids contain 30 to 100 of protein p.p.m. of which 1.0 p.p.m. is fibrinogen. It contains the proteins of blood plasma and in addition nucleoproteins from the broken down cellular elements. The globulin usually exceeds the albumin, the contrary holding true in transudate fluid. In addition there may be present a seromucin precipitable by acetic acid and free of phosphorus.

Salt and extractives are present in transudates and in exudates as in plasma.

Carbohydrate is present in transudates and exudates and true chylous fluids, but absent from pseudochylous fluid except where diabetes exists.

Immune bodies and enzymes have all been demonstrated in the fluids.

Lipoids.—Cholesterin is found in all long standing fluids. In true chylous fluids the lipoids of the fluid vary with the dietary and may reach 17 per cent. Pseudochylous fluid contains little or no fat but high lecithin which with pseudoglobulin gives to the fluid its milky appearance.

Gases CO_2, N and O are present in solution, the CO_2 usually less than blood in simple effusion. In pneumothorax the gas analyses vary with the type of pneumothorax. In open, the air is but slightly modified. In closed pneumothorax without effusion the O is absorbed, the CO_2 varies from 5 to 10 per cent. and the N rises to 90 per cent. Seropneumothorax presents similar figures. In purulent pneumothorax the CO_2 varies between 15 and 20 per cent. with 80 per cent. N and 2.6 per cent. O. The putrid type may have CO_2 of 40 per cent. and in addition contain H (4 per cent.) methane as high as 6.25 per cent. traces of H_2S.

The following tables in summarizing tabulate points of differentiation in the chemistry of fluids:

TABLE I

	TRANSUDATES	EXUDATES
Specific gravity	1010 to 15	1018
Protein	10 to 30 p.p.m	30 to 100 p.p.m.
Coagulation	slow	rapid
Fibrinogen	0.1 p.p.m.	1.0 p.p.m.
Nucleoproteid	0	+
Freezing point	as serum	lower than serum

TABLE II

	CHYLOUS[29]	PSEUDOCHYLOUS
Fat	as diet up to 17 per cent.	little or none
Lecithin		high
Cholesterin		low
Pseudoglobulin		+
COH	+ (but less than plasma)	+ (in diabetes only)

TABLE III

	CO_2, Per cent.	O, Per cent.	N, Per cent.	H, Per cent.	H_2S	Methane, Per cent.
Pneumothorax open	1.76	18	79			
Pneumothorax closed without fluid	5–10	5.0	90			
Pneumothorax serous	8.13	1.26	90			
Pneumothorax purulent	15–20	2.6	79			
Pneumothorax putrid	40	....	..	4	trace	6.25

PATHOLOGY

The normal pleural cavity is lined completely by flattened mesoblastic cells and has richly vascular walls. The cavity, which is of course only potential, contains a small amount of clear fluid. This fluid may be quantitatively increased but qualitatively unchanged without change in the pleural lining similarly in conditions where a mechanical transudate occurs. This is not a pleuritis and will not be further considered.

The simplest and earliest evidence of pleural inflammation is a disappearance of the normal pleural luster and in its stead a dull opaque membrane which when scraped, yields small flakes of fibrin. This constitutes the ordinary dry or fibrinous pleuritis. It is so rarely, if ever, primary in children, that some other intrathoracic lesion, especially in the underlying tissue, must be sought or else a general process. The fibrin may be completely absorbed within 7 to 10 days or the process may be associated with an exudation or fibrosis result.

The exudation of fluid is next to be considered. The differences between this fluid and normal or transudate fluid have already been

noted. Exudate fluid, to the pathologist, is most interesting because of its formed elements. Widal's[35] work on cytodiagnosis, while in the main corroborated, has to be somewhat modified. All these fluids contain fibrin and flat endothelial cells in various states of preservation. The presence of mononuclear cells, taken by Widal as pathognomonic of tuberculosis, must be carefully interpreted. Such cases are undoubtedly most often tuberculous, but it is to be borne in mind that all these are not tuberculous, and contrariwise, all tuberculous fluids do not show mononucleosis. The pleural changes are usually those of the underlying condition, i.e. tuberculosis and tubercles and old adhesions are to be sought. The various appearances of the lymphocytes in differential diagnosis have not been studied in children. Where bacteria are present in the fluid or leukocytes, empyema exists. Here one finds a shaggy thick pleura often separated into cavities by thick bands and containing pus. The interlobar fissures are also to be investigated as the pus may collect here and in no other place. Microscopically, an intact serosa may persist covered by this exudate of fibrin, leukocytes and bacteria. Healing may be complete or fibrous bands may persist. The presence of air does not modify the picture in any way except that, knowing that spontaneous pneumothorax has occurred, miliary tubercles should be sought with great care.[3, 24] In empyema, too, one may be able to demonstrate an area of rupture in a consolidated region. The later lesions of fibrosis are evidenced by the presence of bands crossing and obliterating or dividing the pleural cavity or causing thickening of its wall. The accompanying lesions are always to be sought as pleuritis is infrequently primary and some initial intra- or extra-pleural lesion will usually be found. Resulting lesions are rare and unimportant. Hypertrophy of the right ventricle is slight if present at all. Amyloidosis after old empyemata is no longer frequent and scars of operative interference have replaced it. Atelectasis of the lung above and displaced mediastinum will be present.

BACTERIOLOGY

Exploratory Puncture.—An ordinary 5- or 10-c.c. syringe with a needle somewhat coarser than the ordinary hypodermic, is best suited for aspiration of the chest. It is extremely important that the apparatus work perfectly. To do so, after sterilization and with the needle attached, the suction of fluid must be easy and what is as important, the parts must fit so well that any negative pressure produced by withdrawal of the piston with the needle in solid tissue will cause a snapping back of the piston without the entrance of air. Sucking of air will point conclusively then to either air in the intrapleural space, or aspiration of some structure in continuity with the air tubes or a hollow viscus. The operator should wear sterile gloves and the skin be prepared with iodin.

The site having been selected, and the question of anesthesia decided, the skin is held taut and the needle pushed in slowly. The

resistance must be noted especially. With the first "give," a negative pressure should be created in the barrel and maintained until fluid enters or the needle is withdrawn. Where no fluid is obtained the contents of the lumen of the needle may be expressed as pus, fibrin and solid tissue may be there present. The fluid is then examined grossly as to its turbidity, fibrin flocculi, color, odor, presence of blood or bile, and the specific gravity taken. A microscopic examination of the sediment will reveal the absence or presence of cells, whether these are endothelial, mononuclear, leukocytic or neoplastic. Organisms are then sought by any of the approved stains. Chylous fluids will also present small free fat globules, while in pseudochylous fluids the globules will be larger and seen also in the endothelial cells demonstrating their origin as part of a process of degeneration. All fluids containing leukocytes or organisms should be inoculated on the ordinary media. Clear fluid with mononuclears should be examined more carefully for tuberculosis and injected into guinea pigs. Hematoidin and cholesterin crystals may also be seen. Other examinations are not part of routine and only performed if especially indicated. Pleural eosinophilia has been described but we have not yet encountered it.

Clear Fluids.—By ordinary bacteriological methods the clear fluid obtained by chest aspiration is sterile. Thus at St. Bartholomew's,[2] of 49 fluids examined, 40 were sterile. Clinical evidence and more refined bacteriological evidence point almost to positive proof of the tuberculous origin of most of these fluids. At autopsy 32 of Osler's[2] 131 cases showed tuberculous lesions and 30 out of 95 had positive sputum. Following his cases for five years, Hedges[2] found 40 per cent. with evidences of tuberculosis, and Cabot[23] 117 out of 300. Lord[23] noted a positive tuberculin in 76 per cent. of his cases. Using refined laboratory methods Le Damany[22] obtained 50 out of 55 positive guinea-pig inoculations, and by inoscopy Zebrowski[35] recovered tubercle bacilli in 55 per cent. of his cases.

Streptococcus, pneumococcus and typhoid may also show clear fluid. In early pneumococcus infections clear fluid without cells but laden with pneumococci, may be recovered. Maragliano, by routine puncture, found fluid in 38 of his 58 cases, some of which were purulent, however. Not all these go on to empyema.

Errata in technique and interpretation may give clear fluid. Thus a high puncture, where pus has sedimented, and clear fluid is supernatant, may give clear fluid where pus remains. It is to be always remembered that a clear tap followed by pus may be due to one of two other factors. Thus the operator may introduce infection or a clear pneumococcal fluid may spontaneously become purulent. St. Bartholomew's figures give 7 pneumococcus out of 49, and 2 streptococcus out of 49 clear fluids.

In children, effusion is not common, and is more often pneumococcus than in adults where it is almost uniformly tuberculous.

Turbid fluids are much more frequent than clear fluids in children. Many analyses are available as to the organism. Thus:

	Koplik[19] (212 cases)	Netter[26]	Lord[23]	Babies Hospital[18] (Holt)
Pneumococcus	75	53	39	64
Streptococcus	10	46	20	14
Staphylococcus	6	1	36	8
Tubercle bacilli	2	11	16	½ (with influenza)
Mixed infection	9	..	..	12*

* Two thirds of these showed pneumococci.

The streptococcus is usually the pyogenes and often is a secondary infection on top of a tuberculosis. In the pleuritis seen with the acute exanthemata and rheumatic fever, the fluid is sterile unless mixed infection occurs. Typhoid and gonococci[28] occasionally have been recovered from pleural fluid.

Hemorrhagic fluids, other than traumatic, are infrequent in infancy. The presence of the blood may be simply part of a hemorrhagic diathesis, such as scurvy. In the absence of such a tendency, malignancy, usually a sarcoma or tuberculosis, is to be suspected. Rarely the blood may come from young vascular scar tissue.

Chylous fluid is usually seen where thoracic duct rupture has occurred in its intrathoracic portion, but may occur without anatomical lesion. Its chemistry has already been discussed.

"Pseudochylous" fluid is milky fluid without the chemical characteristics of true chylous fluid, in which no rupture of the lymph vessels has occurred and the turbidity is due to the chemical properties (*q.v.*) of the fluid.

CLASSIFICATION

Though the pathological processes are in a final analysis similar in pleuritis, clinically the cases are usually classified as (1) *dry pleurisy*, where the exudate is fibrinous, (2) pleurisy with serous effusion and (3) empyema or pleurisy with purulent effusion. Any of these may result in fibrous lesions or chronic fibrous pleurisy.

Of these, empyema is by far the most frequent under 10 years. Eighty-two per cent. of St. Bartholomew's cases of pleuritis were of this type. In fact empyema is more frequent under ten than in all other decades together. Fibrinous pleurisy as an independent disease is practically unknown. The remaining cases (18 per cent.) are effusive pleuritis.

The cases clinically are not so clear cut, however, and combinations and borderline cases are frequent. The pleuræ react similarly to all injuries and invaders and the difference is only quantitative except in purulent exudates. In each so-called dry pleurisy there is some fluid and fibrin is to be found in effusion. Where the fibrin is in excess, the term fibrinoserous pleurisy has been used reserving serofibrinous for the fluids that have little fibrin. Such a classification as this usual one is on a basis therefore of pleural reaction to injury irrespective of etiology and is obviously inadequate. We have seen, as in pneumonia, that the reaction may be either fibrinous, serous or purulent, and that inadequacy of an etiological classification is equally obvious. We shall here therefore speak of pleuritis only and discuss under each etiological factor the possible reactions of the pleura and shall group the results of these reactions severally.

ETIOLOGY

The insults to which the pleuræ react consist of every possible injury. The results are infrequently of consequence and usually impossible of detection. The diagnosis of pleurisy is much more often the pathological diagnosis than the clinical diagnosis, and the complication of pleuritis is infrequently of clinical significance in proportion to its presence.

Primary idiopathic pleuritis, found in adults, is a fibrinous process. In infancy and childhood the disease is not encountered and Holt[18] has denied it a place in the independent clinical diseases of childhood. Corroborating this, we have found no case of primary dry pleuritis below 11 years of age in our records at Mount Sinai Hospital.

Age.—Age has a decided bearing upon the type of reaction of the pleuræ, the relative incidence of purulent effusion being extremely high in the earlier years. Thus, at St. Bartholomew's Hospital,[2] 82 per cent. of the empyemata occurred before the age of 10, and of these the average age was 2.1 years. In the records of Mount Sinai Hospital, of 205 cases of empyema, 139 or 68 per cent., were below the age of 11. Of the 174 pleurisies below the age of 11, 80 per cent. were empyema and 35, or 20 per cent., were pleurisy with serous effusion. It is to be borne in mind, however, that these figures are on the basis of clinically distinguishable pleuritis and that while every case of empyema is diagnosed, some fibrinous and serous pleurisies are missed clinically.

Sex.—The higher incidence of pleuritis in males over females is found in all figures. At St. Bartholomew's, the relation was 2.5 male to 1 female. The explanation is probably that of the higher incidence of pneumonia in the male. In our cases the relation was 69 males to 42 females.

Season.—Pleuritis is an all-year-round disease, the maximum in Lord's figures occurring in March.

In our cases, the following distribution was noted:

	Total cases	Percentage of cases	Deaths	Percentage of deaths
January	19	12.0	4	13.0
February	9	5.0	1	3.0
March	13	9.0	5	16.0
April	23	14.0	5	16.0
May	15	10.0	4	13.0
June	21	13.0	4	13.0
July	9	5.0	2	6.5
August	9	5.0	0	0.0
September	4	2.0	0	0.0
October	11	7.5	2	6.5
November	13	9.0	4	13.0
December	12	8.5	0	0.0

Exposure.—The rôle of exposure is difficult to estimate. In most cases on careful questioning, a history of such may be obtained, but the fact of the frequency of similar exposures without pathological effect, renders this information of little or no value.

Injury plays little or no part in the pleuritis of infancy. Certainly the ordinary cases of pleuritis are not the result of injury. Extensive traumata to the chest with hemorrhage or fracture may certainly cause a simple fibrinous or hemorrhagic exudate in the pleural cavity and the entrance of air and organisms from without or through ruptured lung tissue may give rise to such complications as simple or pneumo-, hydro-, hemo-, or pyothorax. These cases are unusual. We have no records of such in children below the age of 11. One type of traumatic pleuritis is fairly frequent. Careful physical examination and especially *x*-ray will reveal in many cases after exploratory[31] or therapeutic paracentesis thoracic a partial or complete pneumothorax.

By Extension.—The presence of any lesion of the adjacent mediastinal tissues is accompanied by a reaction in the overlying pleura, usually fibrinous, but occasionally purulent as determined by the primary intrathoracic lesion. This pleuritis often cannot be detected and seldom is of bearing on the case clinically. Such a lesion may follow primary intrathoracic processes in the esophagus, pericardium, abdomen, lungs or costal structures.

(*a*) *Esophagus.*—Cicatrices from caustics, etc., abscesses may excite an overlying pleuritis or in the case of the latter, burrow into the pleura and encapsulate or rupture into the free pleural cavity.

(*b*) *Pericarditis* is often accompanied by a certain degree of mediastinitis, usually fibrinous, as is the pericardial lesion.

(*c*) *From below* rupture of subdiaphragmatic processes and extension through lymphatics rarely occurs in infancy. Liver abscesses, either amebic or secondary to portal pyemia or peritonitis secondary to

perforation may rupture through the diaphragm, setting up a purulent reaction or acting through the lymphatics, may incite a fibrinous exudate. Such cases are clinically rare and we have encountered none such in our reports.

(*d*) *Lungs and Costal Structures.*—Any pulmonary lesion that is peripheral is accompanied by an overlying pleuritis, the type of reaction depending upon the lung lesion. Thus, bland infarcts and many pneumonias cause merely a fibrinous exudate, though pneumonic processes may be purulent and infrequently serous. Tuberculous lesions are usually fibrinous or serous, and finally fibrous, or, if secondarily infected, purulent. Lung neoplasms and pleural neoplasms, usually sarcomatous, cause an overlying dry pleuritis and almost constantly a hemorrhagic exudate. Osteomyelitis of the vertebræ or ribs has been seen to extend and involve the pleuræ.

(*e*) *Without Demonstrable Intrathoracic Lesion.*—Many cases fall into this group. Careful study, however, excludes many and it is probable that more and more will we be able to limit this class. In many cases of serous effusion, other clinical evidences of disease are absent. At autopsy, however, and in more extensively studied cases, other intrathoracic tuberculous lesions are demonstrable and the probability that such exist in all cases is great but difficult of proof. Many cases, however, defy even careful scrutiny for other lesions. Thus, the pleuritis of nephritis and rheumatic fever, aside from the hydrothorax of cardiac insufficiency, cannot be ascribed to underlying pulmonary lesions. The same may be said for the rare cases reported with gonorrheal arthritis,[28] and after *x*-ray therapy. Whether syphilis of itself may cause a pleuritis is doubted. Certainly cases must be extremely rare.

(*f*) *Bacteria and their products* furnish the vast majority of pleuritic lesions. Of these the most may be ascribed to the *pneumococcus*. Whether the pneumococcus can cause primary pleural lesion is questionable. Often an empyema may mask all other symptoms, so that signs of consolidation are not to be found and the pleural lesions seem to be present alone, but it is probable that such cases are apparent but not real, and at autopsy pulmonary lesions can be found. The pleura in almost every case reacts in pneumonia. The character of the response varies in individuals and in the same individual at different times. Always one can find an overlying fibrinous exudate. Maragliano, in his cases, obtained fluid 38 out of 58 times, but not always in quantity sufficient to be of clinical significance. Infrequently a clear fluid heavily laden with organisms and devoid of pus cells is obtained, and finally, turbid fluid or pus will be found. Individual cases may run the entire gamut from fibrin to fibrinoserous, serofibrinous purulent fluid, and finally fibrous tissue. The cause of the individual variation is not clear. Careful probing in empyemata, however, may reveal an alveolus ruptured into the pleura.

The tubercle bacillus accounts for some of the remaining cases of pleuritis. Of our cases of serous effusion, 19 while in the hospital,

showed other evidences of tuberculosis. Here one finds as with the pneumococcus, an overlying fibrinous or organized pleuritis in virtually every case. The serous reactions are most often tuberculous (*q.v.*).

Streptococcus, usually pyogenes, is found second only in frequency to pneumococcus, and often is associated with pneumococcus. The fluid may be clear rarely, or more often purulent.

Staphylococcus is an infrequent invader in pleural lesions. Invariably the exudate is purulent and secondary most often to a bone focus as part of a generalized staphylococcus bacteriemia or sepsis neonatorum.

Other organisms, such as typhoid bacilli, Bacillus coli communis,[8] gonococcus[28] and Friedländer bacillus have been found, but these are rarities and may be classed as curiosities.

SYMPTOMS

The symptoms presented in pleuritis are dependent upon several factors. They vary with the type of pleural reaction a fibrinous exudate differing widely from an effusion. They differ also with the intensity of the reaction, and the intensity of the underlying process. The symptoms may be local, distant or constitutional.

Local symptoms are pain, tenderness, heat.

Distant symptoms are dyspnea, polypnea, cough, expectoration, vomiting and diarrhea or hiccough, sweating, convulsions and cyanosis.

Constitutional symptoms are fever, malaise and loss of weight and strength, wasting, anemia or prostration, and tachycardia.

The onset of symptoms varies widely and may be described as acute, gradual or latent. Fibrinous pleurisy is most often acute in onset when it is sufficient to be detected at all, but when not clinically demonstrable remains latent throughout. Serous effusions, especially tuberculous, are gradual as a rule, and the symptoms are primarily constitutional and local only later. The onset may be fairly acute. Purulent exudates may be of any variety. When acute, local symptoms are more marked and when gradual local symptoms may be entirely masked or absent. In association with pneumonia, the empyema usually follows after a few days of apyrexia. It may be concomitant with the pneumonia and is then referred to as parapneumonic empyema.[12,30] The course of the latter may be fulminating and rapidly fatal rarely or benign and tend to spontaneous recovery.

Local Symptoms.—Pain in pleuritis is most frequently present in fibrinous forms. Here the pain is sharp in character and increased by pressure and respiration. Its site and radiation may vary widely and confusingly. Often it is local and corresponds exactly to the involved pleura. It may, however, be referred to the clavicular or mammary region or to any of the abdominal quadrants, usually ipsolateral. In the latter situation, especially when accompanied by vomiting, the possibility of diagnostic error is not inconsiderable. The disappearance of pain may be due to one of three possibilities: The fibrin may be absorbed or organized or it may indicate the accumulation of fluid.

The pain in effusive types either serous or purulent, is not characteristic or constant.

Tenderness and heat may prevail over the inflamed portion. If these are marked and accompanied by any bulging or edema, the possibility of empyema must be borne in mind. *Pulsation* may also be encountered in such cases.

Distant Symptoms.—*Dyspnea and polypnea* are often mechanical, as in the case of effusion with displacement of the mediastinum, and are then due to torsion of the vessels and air passages or diminution in the pulmonary surface area. In the fibrinous type, these symptoms are protective and are natural attempts to limit the apposition of the raw pleural surfaces. The symptoms may then be alleviated by splinting the lung with tight strapping after full expiration.

Cough and Expectoration.—Pleuritis alone, especially the fibrinous type, causes a reflex dry, harassing, nonproductive cough. With the rapid accumulation of fluid, cough may follow and is then mucoid or even bloody at the onset. The sputum more often takes on the character of the accompanying disease and may be purulent or rusty, etc. Where empyema ruptures into the bronchus, the sputum will, of course, take on the character of the pus.

Vomiting is a surprisingly frequent symptom of pleural disease and must be reflex in origin. It was present in a great many of our cases at onset, seldom persisting.

Diarrhea is not infrequent and when present, should be suggestive of a purulent effusion. This symptom must also be reflex as autopsies show no lesions in the intestines.

Hiccough is present where the diaphragmatic pleura is involved and is of bad prognostic importance after the first week when the coexisting pulmonary lesion is subsiding.

Sweating points to purulent effusion, though it may be part of a general tuberculous toxemia.

Convulsions and syncope are reflex nervous responses of the unstable infantile cerebrum and while alarming to parents, are usually of no clinical significance.

Cyanosis may be mechanical or toxic. Pressure on mediastinal structures, as in dyspnea and polypnea, may also cause cyanosis, or cyanosis may be present in pneumococcal infections due to the formation of methemaglobin.

Constitutional Symptoms.—*Fever* is a most constant and valuable symptom in pleuritis. In serous effusion the temperature rises gradually, reaching a fastigium of 103°F., seldom higher and persisting usually until the fluid disappears, falling as the fluid absorbs. A normal temperature may be looked upon as a most valuble evidence of the absorption of fluid. In purulent effusion, the temperature rises higher usually. It may be added directly to the temperature due to the pneumonia and is then of a continuous type or it may not manifest itself until the temperature has been normal for a time. It persists usually while the pus persists, but may be normal where encapsulation

of a small exudate is present or where there is a fistula with complete drainage. Post-operative rise of temperature may be reaction or due to rapid absorption through the opened vessels, but if persistent, in the absence of complications, means insufficient drainage.

Malaise, loss of weight and strength, and anemia occur in purulent effusions where the process has been allowed to become subacute or may be present in effusion as part of generalized tuberculosis.

PHYSICAL SIGNS

The physical signs in pleural disease may be: (1) *General*, due to toxemia and associated condition; (2) *mechanical*, due to alterations in the mediastinal topography; or (3) *local*. The local signs are due to either the loss of the normal smoothness of the opposed pleuræ or their separation by media which alter the transmission of sound, i.e., air, fluid or both.

Local Signs. *Inspection.*—No visible alteration may be noted in the chest. Where fluid has collected to a greater extent the *chest seems more prominent*, due to a widening of the interspaces and may seem actually to bulge. Respiratory motion is limited or transmitted and the skin has a characteristic glossy appearance. *Edema of the chest wall* is rare and most often points to empyema. In the rare cases of neglected empyemata local inflammatory signs may be seen, even pulsation.

Mensuration is of little value and may confirm the observations of diminished excursion on one side and fulness.

Palpation.—Where the exudate is fibrinous, a *friction rub* may be palpable. Where separation of the pleura occurs with the intervention of less transmissible media such as fluid or air, fremitus is lost over the fluid and the adjacent atelectatic lung. *Local heat* may be palpable on the affected side. *Skin hyperesthesia* may be present, but is not reliable in these young patients.

Percussion in dry pleurisy may yield little of value except very slight dulness. Over fluid the note is flat or very dull. *Flatness is extremely characteristic and whenever present should be very suggestive of fluid.* The increased resistance to the pleximeter finger is often marked. In simple effusion the upper fluid level is characteristically S-shaped being highest in the axilla.[11] Above the fluid level and adjacent collapsed lung one meets a small band of dull tympany (Skodaic). Over air the note is tympanitic, but less so in infancy than in adults and here, as with other signs of air, the findings are often equivocal. Fluid and air give a dull to flat note over fluid with a level upper limit and tympany above. In purulent effusions where adhesions exist or encapsulation occurs, the fluid does not gravitate and gives signs locally. In simple effusion the signs usually are first at the base, though *x*-ray evidence (*q.v.*) points to a vertical disposition of fluid in the axilla. Dulness to flatness may also prevail over thick pleura. In effusion the Grocco phenomenon[13] of contralateral paravertebral dulness to flatness is very constant.

Auscultation is diagnostic in dry pleurisy. The to and fro scratching râle furnishes the best proof of fibrinous exudate. The râle is more superficial than pulmonary râles and unaffected by cough. Unlike pericardial râles it ceases during apnea. Disappearance of friction rub indicates either absorption or the collection of fluid. Over fluid breath, voice and whisper are diminished to absent. Above fluid levels, the compressed lung will give increased intensity and pitch with tubular quality often, and must not be mistaken for consolida-

FIG. 1.—Roentgen examination of the chest shows a dense homogeneous shadow which occupies the axillary portion of the right chest from apex to base. There is a marked thickening of the interlobar fissure. The roentgen appearance is that of an encapsulated effusion.

tion. Egophony may be heard over fluid. and is constant in children. The alteration in transmission through fluid is only in intensity and the transmitted sound whether vesicular or tubular will, of course, vary with the condition of the underlying lung. Amphoric breath and cracked pot note may be present in children at the apices posteriorly, and have not always the significance attached to them in later life. With the entrance of air and collapse of the lung, breath sounds are absent, or diminished tubular breath is heard over the apex transmitted from the trachea and collapsed lung. Where pulmonary

sounds are heard, complete collapse is not present due either to insufficient quantity of air or adhesions preventing collapse. The succussion note and coin sound in pneumohydrothorax are characteristic. Diminished sounds prevail over fibrous adhesions and thick pleura.

X-ray furnishes one of the most reliable physical signs of pleural effusion and pneumothorax. Simple effusion is seen often as a homogeneous shadow extending vertically in the axilla and dipping into the interlobar fissures (Figs. 1, 5). Increased fluid collects more and more

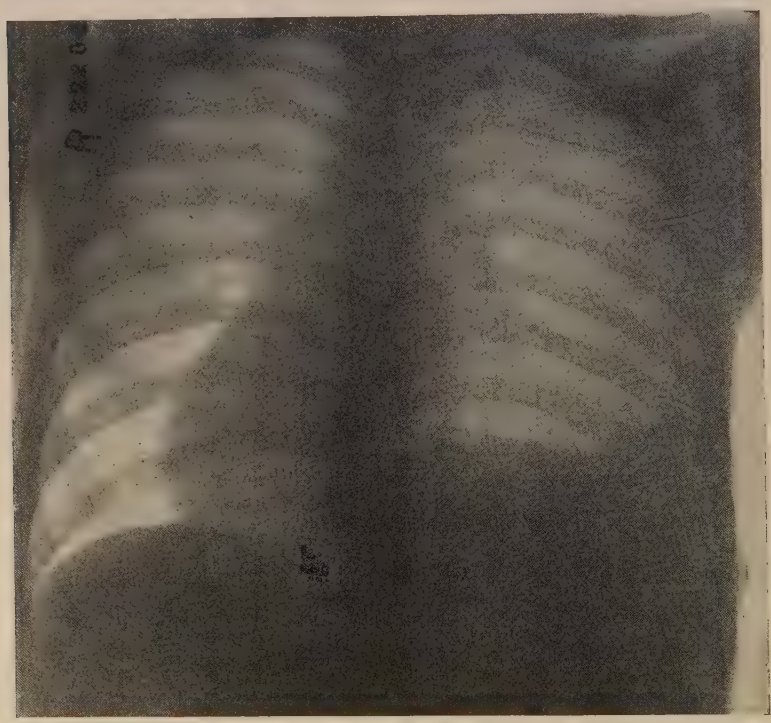

Fig. 2.—Roentgen examination of the chest shows the diaphragm on the right side is somewhat higher than normal, and there is in addition a shadow in the right costophrenic sinus, which is probably due to a small effusion.

at the base and large quantities gravitate to the base with an upper curved limit verifying percussion note (Figs. 2, 3). Encapsulated effusions are less affected by gravity and are represented by dense homogeneous shadows difficult sometimes of differentiation from consolidation, when it often becomes necessary to repeat the *x*-ray in a few days to establish a diagnosis for fluid shadows will remain unchanged (Fig. 3). With the entrance of air and the collapse of the lung, the markings of the pulmonary vessels and tubes will disappear and clear space will prevail (Fig. 4). Fluid and air cause a level upper limit of fluid which shifts with position. Thickened pleura causes an even clouding of pulmonary markings (Fig. 6).

Paracentesis is the only pathognomonic sign of pleural effusion and the most certain differentiation between pus and serous exudate. In children for diagnostic measures it may be carried out with ordinary hypodermic needles without anesthesia or with ethyl chloride. Older children may require cocain. With large effusions the seventh or eighth interspaces below the angle of the scapula may be chosen and the needle plunged in. With experience the condition of the pleura may be indicated by the resistance offered the needle. If such a tap

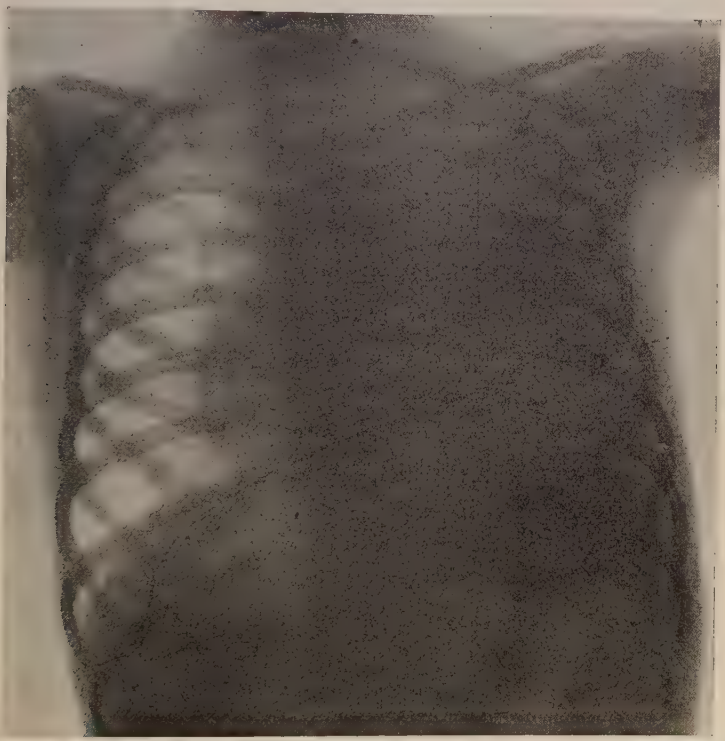

FIG. 3.—Roentgen examination of the chest shows an effusion which occupies the entire left chest from apex to base. The ribs are forced apart and the heart is displaced to the right.

should prove dry, the upper and lower spaces may be tried if one is certain that the needle is patent, not obstructed by fibrin and of sufficient caliber to admit thick pus. Where the pleura is thick, the cavity may not be entered at all, and where the adhesions obliterate the cavity, the needle passes from pleura through lung without ever entering the pleural cavity. A dry tap posteriorly does not exclude the presence of fluid, however, and the axilla may safely be explored in the sixth or seventh spaces to apex of axilla. In small effusions the axilla may be the site of election in the light of *x*-ray evidence of collection of fluid. Where encapsulated pus is suspected, the needle should be thrust into the area of flatness. Fluid so obtained is intrapleural

in origin most often, but may be from a lung abscess or cavity, and has even been obtained from below the diaphragm and pericardium.

Mechanical disturbances in the adjacent lung have been considered. The portion of lung dipping into fluid is usually found collapsed and the entire lung may be pushed toward the hilus and even beyond the midline into the opposite pleural cavity. Rarely it is pushed posteriorly by a large effusion and fluid may not be obtained at the usual site of exploration posteriorly and collapsed lung be entered instead.

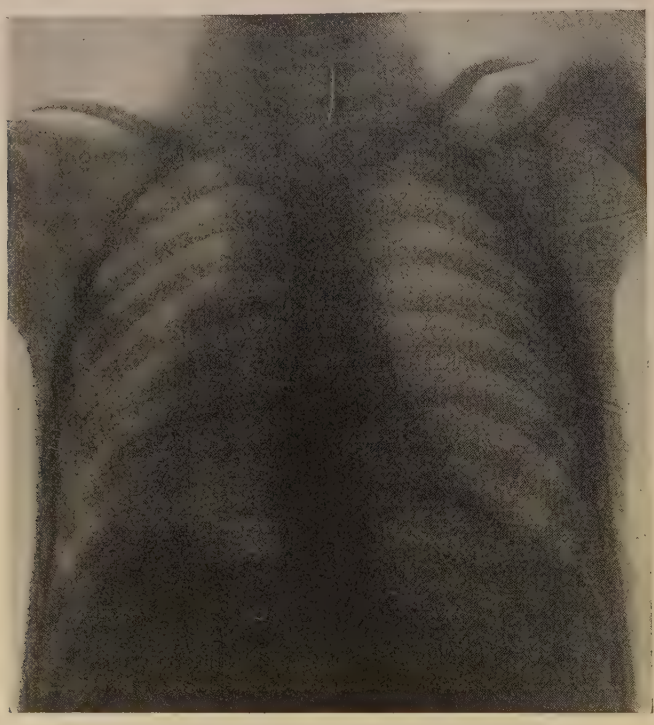

FIG. 4.—Roentgen examination of the chest shows a complete pneumothorax on the right side, the lung being collapsed down close to the mediastinum. There is no evidence of fluid in the right chest. The heart is displaced to the left.

Where adhesions are present, such collapse will be stayed even with the entrance of air.

The heart is pushed over toward the opposite side by even moderate collections of fluid and torsion of its vessels may offer embarrassing symptoms such as cyanosis. Pressure on the veins and lymphatics may work maliciously to diminish the absorption of the collected fluid. With fibrous bands the heart may be pulled to the affected side. Systolic murmurs at the base may be frequently produced.

The liver and spleen may be pushed down by fluid so that the liver becomes palpable. The spleen is rarely to be felt, however, due to simple displacement.

Signs of general infection have already been discussed. The leukocytes show little or no change in simple effusion, but with pus, may rise to 40,000 with a relative increase in leukocytes. The average count in our series in empyemata was 26,000 with 75 per cent. polymorphonuclears and 15,000 in serous effusions with 72 per cent. polymorphonuclears. Blood cultures taken in empyema cases are often positive and the Babies Hospital reports 41 positive out of 88. In

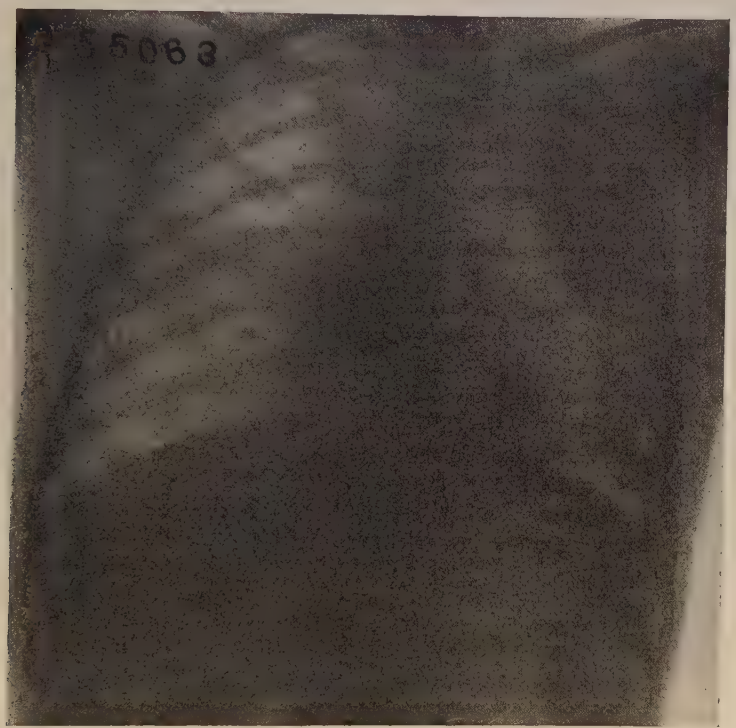

FIG. 5.—Roentgen examination of the chest shows an effusion, which occupies the axillary half of the left chest from the apex to the base. The roentgen appearance is that of an encapsulated effusion.

these, pneumococci were usually found. In protracted empyemata and serous effusions, secondary anemia is frequent. The respirations rise rapidly and the rate of 40 to 70 is not infrequent with pleuritis of any type.

The pupils may be dilated on the side of the lesion due to pleuritis overlying the sympathetic ganglion.

COURSE, COMPLICATIONS AND ASSOCIATED CONDITIONS

Simple fibrinous pleuritis, as has been said, runs no course of its own in infancy. Where it is secondary, it does not affect the course of the underlying condition, and is usually unrecognized. So-called primary serous effusion with sterile fluid and mononucleosis must be

looked upon as presumptive evidence at least of tuberculosis. Where the fluid is aspirated, recurrence is infrequent. Where there is any tendency to absorption, the fluid will usually disappear without aspiration in two weeks, the fall of temperature to normal being the best clinical indication of the restitution to normal. Where fluid shows no tendency to absorb *per se* or actually increases, the withdrawal of

FIG. 6.—Roentgen examination of the chest shows the following changes. The left chest is considerably collapsed, the anterior forepart of the fourth rib is irregular, shows an oval defect and is probably the seat of an inflammatory process. A small piece of bismuth probably injected is seen in the lower part of the left chest. There is seen occupying the lower half of the left chest a uniform shadow which merges above gradually into the lung shadow. When changing the position the upper level of this shadow is not altered. The left diaphragm is abnormally high and seems to be held by adhesions. From the roentgen examination alone it may be said that there is a considerable thickening of the pleura, which has resulted in a retraction of the chest wall. It cannot be stated from the roentgen plate alone whether there is an underlying chronic inflammatory process in the lung or not. This will have to be determined from the clinical history and examination.

some is sufficient to initiate absorption. The fluid absorbs so that it is last present in the axillary position where it is first noted. A redux friction rub may often be obtained. The dulness and signs of atelectasis may persist, however, but the mediastinal displacement is corrected immediately. Rupture of serous fluid is unheard of. Recurrence is infrequent and the course of repeated effusions is apt to be

more drawn out and absorption slower. Sudden death without symptoms has been described, but we have not met with such cases. The development of other evidences of tuberculosis has already been discussed. In those cases where pneumococci are found, the fluid may absorb or become purulent.

The course of purulent fluid should always be interrupted surgically. Absorption is not to be sought for though it is conceivable that such may rarely occur. If surgical measures are not adopted, the pus may become encapsulated or it may rupture internally or externally. Encapsulated effusion may run a long drawn out course for months, giving only constitutional symptoms until surgically removed. Internal rupture with complete evacuation is rare and abscess or gangrene is to be feared. Empyema necessitatis or external rupture leaves an ugly scar, usually in the fifth space in the mammary line, but may drain well. Where air is present in the pleural cavity with serous effusion and the ingress of air at a standstill, absorption of fluid is slower. The absorption of the air is difficult to estimate, but it may absorb in a few days. The presence of air of itself does not alter the course in empyema except as does the underlying condition. Emboli in empyema leading to hemiplegia or brain abscess may occur and formerly when protracted empyemata were seen, amyloid degeneration was seen. Clubbing of the fingers may be noted as early as the second week of an empyema, but is unusual.

The involvement of the other serous surfaces (pericardium and peritoneum) as part of the clinical syndrome known as Pick's disease or polyserositis, is not met with in childhood. We have encountered one case of hemorrhagic nephritis following empyema within six weeks and one case of pyelitis both with recovery eventually. Pneumonia following empyema operations has been frequent occurring in 9 of our 31 fatal cases. Terminal enterocolitis has occurred but once in our series, though diarrhea without intestinal lesion has been frequent at the onset. Peritonitis has complicated one of our fatal cases. Subcutaneous abscess and costal osteomyelitis have followed in but one child, and lung abscess but twice, both cases being fatal. Otitis media has frequently occurred, but of itself seems not to affect the mortality or course once the drum has been incised. Chronic fibrous pleurisy is permanent and usually symptomless.

DIAGNOSIS

Diagnosis of pleural diseases may be divided into three phases. Firstly, it is concerned with the diagnosis of pleuritis, then with the type of pleural reaction, and finally, the etiological factor.

The positive diagnosis of fibrinous pleuritis is the presence of the friction rub. The pain in fibrinous pleuritis, if auscultation is not practiced, may be misleading. If the pain is thoracic, pleurodynia and herpes zoster may be suspected. The former will present no physical signs and the radicular pain, hyperesthesia and eruption characterize the latter. The pain in pneumonia, which is really

pleuritic, may mislead one to make the diagnosis only of pleuritis especially if only the earliest signs of consolidation, i.e., slight dulness and diminished breath sounds be present. The greater dyspnea, leukocytosis and course will point the way to diagnosis and the coexistence should always be suspected in infancy where primary fibrinous pleurisy is so rare. If the pain be abdominal, and especially if vomiting and diarrhea prevail, a surgical abdomen may be suspected. Rigidity and local tenderness will be absent in pleuritis though the tense abdomen of a crying baby may simulate these. The physical findings in the thorax alone are positive and intra-abdominal conditions should never be diagnosed without percussion and auscultation of the chest at least.

An underlying cause for dry pleuritis should always be sought and "primary or idiopathic" must be accepted only by eliminative processes of diagnosis. Where no other findings can be obtained, a tuberculin reaction and complement fixation for tuberculosis should be done.

With effusive pleuritis the aspirating needle alone is proof positive. For the type of effusion and determination of the etiologic factor it is absolutely necessary. The most misleading factor in diagnosis before puncture is the dulness or flatness. If always borne in mind that the intensity alone and neither the pitch nor quality is altered in its transmission through fluid, error will be less frequent. The signs of fluid are most nearly simulated in early erroneously termed central pneumonias, where the only physical sign may be dulness and diminished breath. There will here be found, however, no displacement of the mediastinum, a higher leukocytosis, increased or unchanged fremitus and a later development of signs of consolidation. Needle puncture will be dry or a small amount of fluid may be obtained loaded with pneumococci. Grocco phenomenon is absent and the *x*-ray shadow is not homogeneous and varies from day to day. Where fluid is present, the diagnosis of pneumonia in areas just above fluid level must be made with great reserve bearing in mind the signs of atelectasis above fluid. This diagnosis is difficult and often impossible. Where there is no other consolidation, atelectasis alone will not give the added dyspnea, high leukocytosis, fever and prostration of pneumonia, and the diagnosis rests not so much on the signs as upon the general appearance and reaction of the patient. A huge pericardial effusion may closely simulate a left-sided effusion. The pulmonary signs may be mimicked in every particular and the right border of the pericardial fluid may be mistaken for the displaced mediastinum. The heart sounds, however, will be distant or absent, the apex beat and impulse will disappear, cyanosis and dyspnea will be greater, and the *x*-ray will reveal the true condition. Encapsulated fluid will often simulate consolidation or lung abscess. The presence of flatness should always point the way to fluid, however. Sputum is more copious in the consolidation in older children, but its absence in the young adds to the confusion. Lung abscess may simulate encapsulated

fluid to radiography and exploratory puncture and is then indistinguishable. Thick pleura due to fibrosis or malignancy may simulate effusion, but the absence of mediastinal displacement, the dry tap and the feel of the pleura are leading points. Before paracentesis, the purulent type of fluid may be suspected from the history of preceding pneumonia. The leukocytosis with pus will be higher, and encapsulation more marked, hence, gravitation will often not occur. Serous fluid, except where old adhesions are present, will gravitate.

The diagnosis of the type of fluid rests on the physical and chemical characters as previously outlined. The differentiation of a transudate fluid from an exudate rests entirely upon these factors discussed under Table 1. The differentiation of a chylous from a pseudochylous fluid is chemical.

Cytodiagnosis is of importance in clear fluids. The absence of blood cells and the presence of endothelium only and the characters of an exudate should lead to suspicion of an early pneumococcus fluid, and this will be confirmed by a gram-stain of sediment showing organisms. A mononucleosis in a clear fluid is an almost pathognomonic indication of its tuberculous nature. Purulent fluids will all show a polynucleosis and their differentiation must be made culturally and by stained spread. Sterile fluids on ordinary media should arouse suspicion of tuberculosis and complement fixation and von Pirquet tests should be done. When clear exudate is present and evidences of tuberculosis are absent and rheumatism present, the rheumatic nature of the pleurisy may be suspected. Empyema necessitates must be distinguished from costal or rib abscess and the physical signs should furnish easy differentiation. Pulsating empyema should not be confused with aneurysm, if one bears in mind the infrequency of aneurysm in childhood.

PROGNOSIS

Prognosis in pleural disease, except in empyema, is the prognosis of the underlying disease. Fibrinous pleuritis does not alter the prognosis of the underlying disease and will subside within 10 days. The immediate mortality in effusive pleuritis *per se* is almost inconsiderable. In the Mount Sinai Hospital records, there has been no death reported from effusive pleuritis in children below the age of 11. Sudden death does occur and may follow paracentesis, or a right-sided thrombus or be without autopsy findings. The average stay in the hospital is 33 days. Recurrence points to a poor prognosis as extensive injury of the pleura is usually indicated, due usually to tuberculosis or malignancy. Bloody fluid, excluding trauma, points similarly. Recurrence is infrequent and was found by Cabot to occur in 1.3 per cent. of 300 cases. The danger of the development of active tuberculosis is always to be borne in mind, and Cabot's figures of 39 per cent. of 300 cases in five years reveal this danger. In empyema the pleuritis shows a mortality *per se*. The prognosis here varies with the age of the patient, the organism, the site and the treatment. Under one

year, the mortality is 74 per cent., being 59 per cent. between one and two years and 13 per cent. over two years at the Babies Hospital.[18]

In our own cases of empyema, the following table of incidence and mortality is graphic:

	Empyemata	Over 11 years of age	Deaths	Under 11 years of age	Deaths
1913	34	8	3	26	6
1914	45	18	1	27	6
1915	64	19	3	45	12
1916	62	21	4	41	7
Total	205	66	11	139	31
Per cent	...	32	16	68	22

Analysis of these 31 deaths below 11 years of age reveals the following:

Over 3 years	7 = 22 per cent.
2–3 years	7 = 22 per cent.
1–2 years	12 = 40 per cent.
Under 1 year	5 = 16 per cent.
Total	31

The average age of these children dying as a result of their empyema is one year and nine months. The distribution as to months has already been noted (*q.v.*, etiology).

The high mortality below two years of age is usually due to low resistance, the little patients failing in the third or fourth week despite adequate drainage.

Of the organisms, the pneumococcus offers the best outlook. Streptococci and mixed infections have a high mortality and any tubercular complication is bad prognostically. The surgical treatment, the promptness and adequacy of drainage are of greatest importance and will be best discussed in another place. The end result after the subsidence of empyemata is surprisingly good. The expansion of the lung is prompt usually and complete. The presence of fibrous lesions is rarely of clinical significance. The question of sinuses and pus pockets will be discussed elsewhere.

We find but three cases of bilateral empyema in our series, two of whom died. The post-operative mortality of empyema is not exclusively surgical, however. In our cases (31) previously referred to, nine developed pneumonia, of whom three had also an associated otitis media, one a colitis and one measles. Besides pneumonia, we find one with an associated diphtheria and two with lung abscess,

so that 12 of the 31 fatalities suffered also a complicating medical condition.

TREATMENT

There is no prophylactic or specific treatment for any of the types of pleuritis and we must be content to treat symptoms.

In dry pleurisy, pain alone requires attention. In older children, tight adhesive strapping after full expiration will afford relief but often with these older and always with younger children, the tender skins limit the use of counterirritation. Leeches, mustard, cupping and other preparations, are to be avoided as the presence of first and second degree burns is not rare. Heat, in the form of water bottles and rubber bags or compresses, combined with oral therapy, will usually give relief. By mouth, salicylates usually acetyl salicylic acid (aspirin) or small doses of codein, surely will mitigate pain.

The treatment of most of the symptoms of effusive pleuritis is by paracentesis thoracic. Instant and complete removal of any amount of fluid in the chest is no longer advocated. In tuberculosis of the lungs, the presence of fluid has even been thought of therapeutic value, acting mechanically as the insoluble N. in artificial pneumothorax and furnishing antibodies. Certain it is that removal of fluid where there were underlying pulmonary lesions has been followed by a severe flare-up of the tuberculosis.[20]

Indications for Chest Aspiration.—(1) Where the mechanical difficulties are great either because the collection has been sudden, but not necessarily great, or where the collection is extensive causing cyanosis, dyspnea, etc.

2. Where absorption is slow and no progress is seen for 7 to 10 days.

3. Where previous paracentesis thoracis has been performed.

Where to Perform.—Where the effusion is large and gravitation has occurred, the space below the angle of the scapula is the site of election. Where bands, etc., limit gravitation, the area of greatest flatness should be sought and the space sought where fluid was obtained diagnostically. With small effusions the axilla in the sixth space may be tried safely.

How to Perform.—Strict asepsis should prevail. The operator should scrub up as for any major surgical procedure and wear sterile gloves. The skin area is painted widely with iodin and the space chosen with the patient's arm at the side in the erect posture. The patient's arm is then held over the head. The operator then inserts his finger between the ribs so as to widen the interspace, and the skin being held taut, the needle is plunged above the lower rib. The apparatus used should be any of the various methods which takes off the fluid and prevents the entrance of air. The Potain apparatus is commonly used in our wards. The apparatus consists of a large bottle with a two-holed rubber stop cock. One of these leads to the needle, the other to a large syringe with which to exhaust the bottle. The stop cock to the needle is closed and the bottle is exhausted. The

stop cock to the exhaust is then closed and after the needle has been plunged in, its stop cock opened and flow established. Stimulation trays should be at hand during these procedures, and aromatic spirits or a hypodermic of caffein or camphor given, if necessary.

When to Stop.—The presence of bloody or serous expectoration or severe pain should be an indication to stop. With faintness and with teasing cough, the flow should be interrupted temporarily or the flow slowed by pinching the rubber tube. Attempts to withdraw every drop of fluid are futile, as removal of much fluid will be followed by absorption of the remainder.

Dangers.[6]—Sudden death without lesion or due to emboli has occurred, but is rare. Death in shock after 24 to 48 hours is also reported. Where intrapleural tension and mediastinal pressure has been greatly and rapidly altered these are more likely and hence it is advisable to withdraw fluid slowly. Neither should both chests be aspirated simultaneously, but alternately, and at as wide intervals as possible.

Injury to the lung and pericardium in these little patients must be frequent, but are of little significance. Where there is purulent infection, however, of pulmonary tissue, the previously sterile cavity may become infected upon withdrawal of the needle, but this too is infrequent. Hemorrhage from the intercostals may be avoided by entering above the lower rib. Entrance of air is frequent and of no importance.

Injections either into tissues or cavity of air (1) and adrenalin have been used to prevent recurrence, but as so few recur anyway, the value of these measures is difficult to estimate and they themselves seem to us unnecessary.

Eliminative measures by purging and limiting fluid intake are of no avail and greatly distress the patients.

Potassium iodide is often given but its value as an aid to absorption is difficult of proof.

Hygienic Measures.—These patients should be kept abed, preferably near a window, at least until the temperature is again normal. They should be kept quiet for at least 48 hours after aspiration, and flat in bed for the first 24 hours. Exercises involving chest expansion should be instituted later.

The treatment of pneumothorax combined with serum or pus is the treatment of the serum or pus alone. The treatment of pneumothorax alone should in general be expectant of tuberculosis if spontaneous. If the entrance of air be traumatic, the treatment is for the mechanical disturbance or failure of absorption. Where the egress is greater or equal to the ingress, no measures are necessary. Where the egress is less than the ingress and a valvular condition prevails, the mechanical disturbances may demand a widening of the egress or a formation of an additional point of egress in the wall as a lifesaving measure at times. Spontaneous pneumothorax may, as with spontaneous effusion, actually quiet a pulmonary tuberculous lesion.

The treatment of empyema is surgical and immediate. The coöperation of the surgeon is of great help to the little patient. Where it is suspected that pus will be withdrawn, the surgeon himself should be asked to perform the aspiration or should be present. This is for two purposes: Primarily, he sees the site of puncture as a guide to incision, and secondarily, that the operation may be performed without delay, so that the order is given that these patients be prepared for operation before aspiration is performed. The after treatment of all forms of pleuritis and post-operative care are general hygienic measures of forced feedings, fresh air and exercises to promote chest expansion. Supportive treatment, where wasting has occurred, is useful.

Autoserotherapy[9] has been tried here as in almost all other lesions where something to inject has been available. It is without rationale and its use is to be depreciated as the probability of introducing infection into otherwise sterile tissues is always present.

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CHAPTER LXIII

ABSCESS OF THE LUNG

By Henry Heiman, M.D.

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The cases of lung abscess in children are strikingly few. Holt[5] records having seen only three. We do not include numerous minute foci of suppuration very often found as a termination of acute bronchopneumonia. In studying the case histories of about 4500 children treated in the Pediatric Service at Mount Sinai Hospital during the past five years, we have found five. On the adult wards it is not a very uncommon condition. In view of the numerous operations performed upon the nasopharynx of the young, its infrequency is surprising indeed.

Etiology.—Primary abscess of the lung very seldom occurs. It generally develops as a result of one of numerous conditions. These may be grouped into four classes:

1. Metapneumonic
2. Disease in a contiguous region
3. Embolic
4. Pulmonary tuberculosis.

The metapneumonic include those following lobar, broncho and aspiration pneumonias. Influenzal pneumonia is not an uncommon cause. Of 49 cases, all ages, collected by Tuffier,[10] 23 were metapneumonic.

Aspiration pneumonias follow operations upon tonsils and adenoids and conditions which produce paralysis of deglutition. Two of our cases resulted from lobar pneumonia. Two others developed upon aspiration pneumonias. Orth and Silberman[6] reported a number of cases in very early life which they suggest might have resulted from inhalation of infected vaginal secretion during birth.

Lung abscess may be produced by contiguity from localized empyema or from suppurating bronchial lymph-nodes. In this group may be included perforation of the esophagus from injury and abscess formation which involves the lung.

Of the embolic causes the most common in children are chronic otitis media[7] and infective endocarditis.

Pulmonary tuberculosis is rarely complicated by lung abscess.

Suppurating hydatid cysts have not been reported in children.

Bacteriology.—A number of organisms have been isolated, very commonly two or three varieties may be found in the same case. The influenza bacillus with streptococcus and staphylococcus aureus are frequent invaders. Pneumococcus is not uncommon. In aspiration

cases, Bacterium coli and Bacillus subtilis have been isolated as well as anerobic organisms.

Pathology.—The figures of Tuffier give 80 per cent. occurring in the lower lobe. Three of our cases involved the lower lobes, one the upper, and another, both upper and lower lobes. Abscesses of the lung, unless they are infected cysts, never have a well defined lining membrane. The appearance is honey-combed and sponge-like, surrounded by consolidated lung in recent cases and fibrotic dense tissue in chronic ones. Microscopically, all our cases showed simply typical purulent suppurating tissue with slight dilatation of smaller bronchioles.

Symptoms.—In children, the symptoms and signs are generally much less characteristic than in adults, so that the diagnosis has rarely been made before operation or on the autopsy table.

There is commonly a history of a previous pneumonia followed by a persistent cough with remittent periods of fever and "grippe" sensations; or of an operation in the pharynx with obstinate chronic cough following. Occasionally, we get a definite history of aspiration of a foreign body.

One of our cases, (L. F.) a child eight years of age, had a history of two attacks of pneumonia seven months previous to admission to the hospital, followed by severe, persistent unproductive cough. No febrile periods were mentioned. During his first week in the hospital, the temperature was intermittent, between 100 and 105°F., with respirations of 40 to 60.

A second case (S. G.) six and one-half years of age, gave a history of bronchopneumonia two and one-half years before admission. It was only during the last seven months that a chronic cough developed with profuse foul smelling expectoration.

V. H., a girl three and one-half years of age, aspirated several pieces of nut kernel one year before admission, which were removed at once by bronchoscopy. Three months later cough developed and soon after, foul smelling expectoration and fever. Five weeks before coming to the hospital, an attack of acute pneumonia was contracted.

Another case (V. H.) gave a history of tonsillectomy one and one-half years before admission to the hospital, followed by remittent cough.

Expectoration of foul smelling sputum is not to be relied upon in children, as in adults, as this symptom is frequently absent.

Fever varies considerably, sometimes it is septic in character, in other cases the temperature is normal.

Moderate leukocytosis (15,000 to 20,000) is generally present.

While hemoptysis occurred in one of our cases, it is a very unusual symptom.

Clubbing of the fingers is not an uncommon sign, especially in chronic cases. It was noted in the histories of two of our cases.

Signs.—Physical signs are not at all characteristic. They vary widely, probably depending upon the quantity of fluid and consolida-

tion about the abscess. All one may obtain over a large area of involvement is moderate dulness and diminished vesicular breathing. In other cases there are definite bronchial breathing and râles. Occasionally one gets all the typical signs of cavitation.

Diagnosis.—The diagnosis is extremely difficult. In three of our cases it was not made before operation. The diagnosis usually made is bronchiectasis or empyema.

Profuse expectoration of pus and the presence of elastic tissue in the sputum are the strongest evidences of the presence of an abscess.

The Roentgen ray is very helpful in making a diagnosis. At times one may get definite evidence of cavitation with fluid level, but in our cases the *x*-ray examinations revealed only persistent dense shadows.

Bronchoscopy is a valuable aid in diagnosis, and in exact localization of the lesion. But this procedure should seldom be resorted to in children as it entails with them the use of a general anesthetic.

Complications.—Serous or purulent pleural effusion may develop either by irritation or actual rupture. Pyopneumothorax[9] has been reported.

Cerebral abscess from embolus may occur. Dix[2] has reported a fatal case.

Treatment.—Inhalations of creosote and turpentine have been used with some relief. Creosote by mouth has been used. The question of operative interference should always be considered. Our five cases came to operation. Two cases responded after thoracotomy and incision of abscess with drainage, and were discharged well. Two others received partial pneumectomies with very good results. One case proved fatal after operation. Here there was an extensive involvement of both upper and lower lobes and practically the entire lung was excised.

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CHAPTER LXIV

GANGRENE OF THE LUNG

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Gangrene of the lung in children is very rarely diagnosed. Perkins[8] states that it is comparatively rare in childhood. The diagnosis has not been made ante-mortem in any of our 4500 cases during the past five years. In the autopsy room in several cases we have seen small areas of gangrene in association with pneumonic consolidation.

Etiology.—The predisposing causes in children are malnutrition, infectious fevers, especially measles and influenza, and rarely diabetes.

It may follow:

1. Lung conditions, *e.g.*, acute lobar or bronchopneumonia, aspiration pneumonia, fetid bronchitis, bronchiectasis or tuberculosis.

2. Embolism, more frequently from otogenous conditions. L. Gullemot[3] has reported such a case in an infant seven months of age, and Rehm and Horand in a child six years of age.

3. Injury from contusion or penetrating wound.

In a report of 5072 autopsies upon individuals of all ages, Hensel[4] found the condition present in 83 cases in association with lobar pneumonia 8, tuberculosis 11, embolism 26, carcinoma 10, bronchiectasis 5, cachexia 5, aspiration 9, injury 3.

As to the relation of pneumonia to gangrene, there have been varying opinions as to whether or not the former always precedes the latter condition. It seems to us that no such strict rule can be laid down.

Pathology.—Gangrene signifies a putrefaction of necrotic areas. There are two well recognized forms, the circumscribed, which is commonly seen, and the diffuse, which is extremely rare. The latter has no limiting area of lung consolidation.

Three stages have been described:

1. Recent mortification. The area involved is moist but fairly firm and green in color.

2. Liquifaction during which the necrotic area is broken down into a spongy mass.

3. Excavation or the formation of necrotic cavities.

Bacteriology.—In this condition, numerous organisms have been isolated, but not one has been found to be alone responsible for the development of the condition. Among those described are sarcinæ, Infusoria, proteus, leptothrix buccalis and definitely pathogenic bacteria, as streptococcus, staphylococcus and pneumococcus. Anaërobic organisms are very frequently found.

Symptoms.—In children the characteristic picture so seldom develops before death, that the diagnosis is rarely made. The gangrenous odor of the breath and profuse expectoration of necrotic tissue are typical of the disease. The sputum forms three layers, the lowest purulent and containing white masses composed of fatty acids, the middle, fluid, and the upper frothy. Elastic tissue is not as frequently found as in abscess.

Septic temperatures and marked prostration are common.

Profuse hemorrhages are not an unusual manifestation of the destructive process.

Signs.—Physical signs may vary a great deal with the changing conditions in the lung. In the diffuse form one may get over a wide area, dulness and bronchial breathing with large moist râles. In the circumscribed form less marked signs are present. With excavation we may elicit signs of cavity.

The Roentgen-ray is very helpful in the localization of the lesion, in determining its extent, and at times the stage of activity.

Complications.—Pleurisy and empyema are not infrequent complications. A case of pyopneumothorax following gangrene of the lung in a child three and one-half years of age has been reported.

Cerebral abscess must be considered as a possible complication.

Treatment.—For prophylaxis one must watch carefully the nutrition of the undernourished child during an acute infection. Its resistance should be increased by every known means. When the condition develops, inhalation of creosote and turpentine should be used. Intra-tracheal injections have been tried with some success. The grave danger from operative interference in these cases is fatal hemorrhage.

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CHAPTER LXV

INFARCTION OF THE LUNG—PULMONARY FIBROSIS—ECHINOCOCCUS OF THE LUNG—SUBCUTANEOUS EMPHYSEMA—MALFORMATIONS OF THE LUNG—TUMORS AND CYSTS OF THE LUNG

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INFARCTION OF THE LUNG

Infarction of the lung in children may be due to thrombosis or to embolism, the latter being the more frequent cause. If the infarct is embolic in origin, whether it will be bland or septic will depend upon the character of the thrombus from which the embolus is derived. Because of the anatomical relationships of the pulmonary vascular system, infarcts of the lung are of the hemorrhagic type. They are usually subpleural, wedge shaped, with the base of the lesion at the pleural surface. They may vary in size from a few millimeters in diameter to large areas which occupy the greater part of a lobe. Small infarcts are often multiple. They occur more frequently in the lower lobes, and more often on the right than on the left side. The early infarct appears as a dark red, firm, airless, slightly swollen area of varying size beneath the pleura. On section it is dark red, often almost tarry in color, rather dry, and not granular. The margins are indistinct and the immediately surrounding tissue is edematous and contains bloody fluid. The occluded vessel may be present at the apex or in the center of the area. If the lesion is a bland one, it becomes browner and lighter in color as the blood pigment becomes broken down and the tissue becomes moister. Organization may transform the area into a fibrous nodule, or liquefaction with expectoration or absorption of the fluid may transform it into a cavity. If the infarct is a septic one, the area of infarction becomes surrounded by a zone of pneumonia and the infarct itself is transformed into an abscess or becomes gangrenous.

Bland infarction most often follows marantic thrombosis of the dural sinuses. Cases have been reported following thrombosis in the cardiac auricles or ventricles, in the inferior cava, and in the femoral vein. Peculiar to lung infarction in the early days of life is its relation to thrombosis of the ductus arteriosus. Septic lung infarction most often follows purulent thrombosis of the transverse sinus due to disease of the middle ear or mastoid. In the first days of life inflammation of the umbilicus with purulent thrombosis of the vein may lead to septic infarction. Infected cephalhematoma with

thrombosis of the veins of the diploe has also been reported as a cause of pulmonary infarction. The condition may be the result of thrombosis which is primary in the pulmonary artery; Lutz has called attention to the relative frequency with which pulmonary artery thrombosis occurs in measles in very young children. In 22 autopsies on infants dying at one to one and one-half years, he found thrombosis eight times, six times of the pulmonary artery. Compression of the vessels of the lung by intrathoracic tumors, or even by intra-abdominal conditions, may lead to infarction. Vessel occlusion by white blood-cells may occur in leukemia.

The clinical manifestations in children are much like those of pneumonia and atelectasis, two conditions which must be considered in the differential diagnosis. The temperature increase which may occur at the onset of infarction is of short duration if the lesion is a bland one. Since septic infarction results in pneumonia, abscess or gangrene, the diagnosis of the embolic nature of the process must rest largely upon the discovery of a primary focus from which infective material may be derived.

PULMONARY FIBROSIS

"There are those, like Stofella, in whose opinion interstitial pneumonia is never primary, or, like Eichhorst, who believe it is mostly secondary." These words, with which Abraham Jacobi, in 1902, opened an address upon "Peribronchitis and Interstitial Pneumonia," are still applicable today as an expression of the prevailing opinion upon this subject. The pathologic anatomist seeks to explain fibrosis of the lung as the result of some antecedent condition. Clinically, induration of the lung is most often an end stage of some acute involvement. But there still remains the possibility that in rare cases the stroma of the lung may increase progressively in amount without the stimulus of a known acute process. Jacobi, in the address mentioned above, is one of the strongest proponents of this possibility, and concludes that "so-called interstitial pneumonia . . . is a frequent and frequently independent disease." According to him it has its origin in childhood, but is discovered most often in later adult life. Most often the apex of the right lung is involved and the symptoms and physical findings are such as to lead to a suspicion of tuberculosis. Taking its origin from the stroma of the interlobular septa and of the bronchi, in part also of the apical pleura, the connective tissue as it is laid down compresses alveoli and obliterates them by progressive involvement of alveolar septa. Some of the apical alveoli may undergo compensatory emphysema. The small bronchioles become dilated and their walls and the immediately surrounding tissue are infiltrated by lymphocytes. The result is an indurated, scarred, partially retracted apex, which the pathologist lists as a healed tuberculosis. While the scarred apex, as it is encountered at autopsy, is probably most often the result of tuberculosis, one does see cases in which the fibrosis invades the apex rather diffusely and in which no histological

evidence of tuberculosis can be detected. As Jacobi points out, cases of apical interstitial pneumonia of the type which he considers primary, may continue for years without presenting clinical evidence of tuberculosis and the majority "get well, if not anatomically, still practically."

If we grant that apical fibrosis, not due to tuberculosis, occurs, we are still forced to seek an explanation of the initiation of the process. Although Jacobi prefers to speak of the condition as an" interstitial hyperplasia," this gives no insight into the cause of the connective tissue proliferation and does not establish that the fibrosis was the primary condition. One demands a cause for proliferation of stroma. Jacobi states that some of the cases have a rather acute onset. In these, low grade inflammation of the terminal bronchioles of the apex may be the beginning of the lesion. In cases which have an insidious

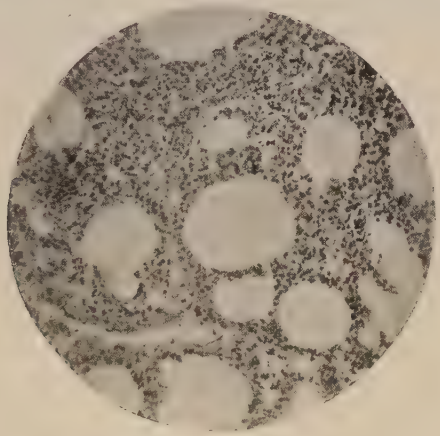

FIG. 7.—Chronic interstitial pneumonia of marasmus. Hematoxylin and eosin. × 100.

onset, the initiation of the process may be a localized atelectasis of the apex, the stroma proliferation following collapse of alveoli and being continued by the bronchiectasis established by the shrinkage of tissue.

Localized fibrosis of portions of lung other than the apex may also apparently occur. Riesman has described a clinical condition in children and young adults, which is characterized by insidious onset without evidence of acute pneumonia, and by fever of a low grade which may run a protracted course of three or four months. There is slight dulness at the base, one side alone being involved, the left more often than the right. The actual anatomical changes are not known, the cases ending in recovery with complete restitution of normal physical findings. Riesman terms the process a "lobar form of bronchopneumonia," and considers it chronic inflammatory from the beginning and possibly due to the pneumococcous. While neither the pathology nor the etiology of the condition may be considered as established, its duration would indicate proliferative changes upon the part of the

stroma of the lung. Schultz has called attention to the occurrence of fibrosis of the posterior and basal portions of the lungs in infants dying of marasmus. Histologically the condition may simulate the interstitial pneumonia of congenital syphilis so closely that only the absence of treponemata permits one to decide that the condition is nonluetic. Atelectasis and passive hypostatic congestion may be the underlying factors in the stroma proliferation. The localization of this chronic process is like that of the acute paravertebral pneumonia of marasmatic nurslings described by Czerny, according to whom hypostatic congestion due to decreased intra-abdominal tension is the essential factor, both in localization and infection.

The proliferative changes which characterize idiopathic bronchitis obliterans, first described as a clinical and pathological entity by Lange, might also lead to fibrosis of the lungs in cases of sufficiently long duration. In one of Lange's two cases symptoms had been present for five months before death. Fraënkel, as the result of study of his case of this condition, which was due to the inhalation of irritant fumes, suggests that peribronchial proliferation of the type described may be the cause of fibrotic changes in cases which might have a more insidious onset and more protracted course and which would have to be considered examples of indurative pneumonia. Hart, in a discussion of the origin of the connective tissues in bronchitis obliterans and in pulmonary induration in general, concludes that the chief source of the fibrous tissue is the stroma of the bronchial walls and that the stimulus to proliferation arises in the peribronchial lymphatic channels. He believes that the same process may be operative in chronic inflammations of the lung of apparently primary nature. Galdi, under the designation of pneumonia desquamativa obliterans, has reported a case of interstitial pneumonia of rather widespread lobular distribution, which seems to give the transition between obliterative bronchitis and interstitial pneumonia. Klopstock has described a case, apparently the only one in literature, in which there was widespread, diffuse proliferation of the interstitial tissue of both lungs, rendering them almost airless. The patient was a girl of 10 years, the condition had come on gradually and had become progressively worse, and there was no history of preceding acute condition. Clinically there was marked dyspnea and cyanosis. Syphilis and tuberculosis were excluded as possible factors in the etiology of the condition.

ECHINOCOCCUS OF THE LUNG

Human infection by the cystic stage of the hydatid tapeworm, Echinococcus granulosus (Tenia echinococcus), is rare in this country. It is a disease usually of the age period of 20 to 40 years, and even in those countries where it is much more prevalent than here, it is much less frequent in children than in adults. In regions where it is endemic the proportion of cases in children varies from 4 to 8 per cent. of the total cases for Iceland to 13.9 per cent. for Argentina. Not only is the disease rare in children, but involvement of the lung is one of its

unusual manifestations in children. Klose was able to collect from the literature 62 cases of hydatid disease in children, in only four of which the lung alone was involved, in two others the lung together with the liver, and in one the pleura. The adult stage of the cestode is an intestinal parasite of the dog, so that the incidence of the infection might be expected to be greater among children than among adults. Possibly the relative infrequency of the disease in children where it is endemic is merely an infrequency of clinical manifestations. As a matter of fact, Dévé, who has written so extensively upon echinococcus infection, insists that the infection is contracted during infancy or childhood, and that in those cases in which it does not manifest itself until the third or fourth decade of life the condition has remained latent. Dévé's point is important, since the hydatid cyst of ages up to 15 years is usually a simple cyst, which is much more amenable to surgical treatment than the complicated, often infected cysts of later years with their numerous daughter and grand-daughter cysts.

Localization in the Lung.—The lung may be involved by rupture of a liver hydatid into the lung, usually the lower right lobe; or by metastasis from a primary cyst elsewhere; or the lung itself may be the primary point of localization.

Primary Hydatid of the Lung.—When the lung is involved in infancy or childhood, it is usually the primary focus. The embryo has reached the lung, after its development in the intestine, by the blood or lymph circulation. Arrived in the lung, it undergoes further development, resulting in the formation of a single cyst. The latter is at first simple, and in the lung the thickness of the connective tissue capsule about the cyst is usually less than in the other organs. The cyst develops slowly, possibly for several years without causing symptoms. When the latter develop they are such as to lead to the thought of pulmonary tuberculosis. In the case reported by Archangelsky, symptoms had been present for six years. The diagnosis cannot be definitely established unless the cyst ruptures, so that hooklets, scolices, or portions of cyst membrane are found in the sputum. Rupture may result in immediate death, which has been ascribed to asphyxiation by pieces of membrane; possibly acute intoxication, of an anaphylactic nature, which has been known to follow diagnostic puncture of hydatid cysts, may be the cause of death. After rupture of the primary cyst, secondary ones may develop along the course of the bronchi, and these as well as the remnants of the original cyst may go on to daughter cyst formation. The treatment should be surgical and should be undertaken as early as possible, before the cyst has become complicated. Early diagnosis, therefore, is imperative. *X*-ray, fluoroscopy, and bronchoscopy may be of aid in establishing the diagnosis. Behrenroth considers the *x*-ray findings in early cases characteristic. The shadow of the cyst is circular and sharply defined. Axhausen has also emphasized the need for early diagnosis, for which he considers the *x*-ray and complement fixation of the greatest value. For complement fixation some authors claim that the reaction is positive in

90 per cent. of cases; others that false reactions may be obtained in infestation by other tenia parasites (Kolmer). Eosinophilia may be present, but too great importance must not be attached to this finding unless intestinal parasitism can be excluded. The symptoms are those of the local lesions, together with evidences of chronic intoxication, the so-called hydatid cachexia or phthisis, supposedly due to dialysis of cyst contents through the wall, and characterized by malnutrition, anemia, and pigmentation and dryness of the skin. The symptomatology has been discussed in detail by Behrenroth.

Metastatic Hydatid of the Lung.—Rupture into the venous system of a cyst situated elsewhere than in the lung may lead to metastatic hydatid disease of the lungs. Rupture and mestastasis usually occur in older cysts, hence metastatic pulmonary involvement is rare before 15 years of age. In a series of 14 cases of pulmonary hydatid, Dévé and Mme. Boppe found the pulmonary condition to be secondary to hydatid of the heart in 10 cases. In a series of 28 cases of metastatic hydatid disease collected by Dévé, the metastasis was central, i.e., by the venous circulation, in 17. In 13 of these the primary cyst was in the right heart, and in every one of these the secondary lesions were in the lung. As compared with primary hydatid of the lung, the metastatic form of the disease is characterized by multiplicity of cysts, relative smallness and uniformity of size of cysts, bilateral distribution, and localization in the peripheral, subpleural portions of the lung. The duration of the disease after mestastasis is shorter than in primary cases, no case of metastatic involvement living longer than three years after the development of pulmonary symptoms.

Direct Involvement of the Lung from the Liver.—When a cyst of the liver, which is the organ most frequently involved primarily (50.8 per cent. in a total of 3055 cases at all ages (Klose), ruptures into the lung, the destruction of lung tissue may be rapid and scolices and hooklets may be found in the sputum early. The presence of bile and of bile salts in the sputum may establish the relation of the lung lesion to that of the liver.

SUBCUTANEOUS EMPHYSEMA

The presence of air or gas in the subcutaneous tissues may be due to cellulitis caused by gas forming bacteria, or to a break in the continuity of organs which normally contain air or gas. In the first case the condition is an essential part of an infectious process; in the second, it is a purely mechanical process, in which later bacterial invasion may, but rarely does, become a complicating factor. Organ systems which normally contain air or gas, which, under proper mechanical conditions, may be transferred to the subcutaneous tissues, are the gastro-intestinal and the respiratory. Only the relationship of the latter to subcutaneous emphysema will be considered here.

Escape of air from the respiratory system into the subcutaneous tissues presupposes a break in continuity, and this lesion may be anywhere in the respiratory tract (Comby). Emphysema following

involvement of the nasal fossæ or accessory sinuses is rare. It may follow operation for the removal of adenoids (Gittings) or of tonsils, or sloughing of the tonsils due to infection (Griffith). It is comparatively frequent after intubation or tracheotomy (Josias), when the involvement of the subcutaneous tissues may remain more or less localized to the region of the neck or may become more wide-spread. The occurrence of the condition after intubation does not necessarily

FIG. 8.—Emphysema cutis. (Herman B. Sheffield, in Medical Record, Nov. 25, 1911.)

establish that the lesion was high up and due to intubation, since a concomitant lung condition may be the direct cause of the escape of air. In Herriot's case, however, the proof that the emphysema was the result of rupture of the lung rather than of the intubation does not appear to be clearly enough established. Ulceration of the bronchi due to the presence of a foreign body may be the lesion which leads to the escape of air. Most often the lesion is in the lung, and the most marked grades of subcutaneous emphysema are those associated with pulmonary lesions.

In this more important group of cases due to pulmonary involvement, it is not always possible to find the lesion by means of which the air escaped, nor is it always possible to demonstrate the path taken by the air after it has made its escape from the lung. A number of reports ascribe rupture of the lung as the cause of the escape of air, the inference being that a subpleural air space had broken through the pleura. It must be quite evident, however, that such a lesion, in itself and without pleural adhesions, would cause pneumothorax and not subcutaneous emphysema. Usually the mediastinal tissues are also emphysematous, manifested clinically by decrease in or absence of the area of cardiac dulness, indicating that the air reaches the subcutaneous tissues not transpleurally but subpleurally and by way of the mediastinum. In some cases rupture of emphysematous subpleural alveoli, without rupture of the pleura, has been described, the escaping air making its way with each inspiration beneath the visceral pleura to the hilus of the lung. Interstitial emphysema, characterized by the presence of multiple small air blebs in the interlobular septa beneath the pleura, is said to be not infrequent in children (Ribbert), but association of this process with subcutaneous emphysema is not often seen. While interstitial emphysema may lead to the escape of air subpleurally into the mediastinum, this is apparently a more circuitous path than the escaped air usually takes. In Mackenzie's case air blebs were present beneath the pleura, and free air was present in the mediastinal tissues, but that the air travelled beneath the pleura to the hilus of the lung was not established. Gielczýnski, reporting a case in a six months' old infant with bronchopneumonia, concluded that the escape of air was due to rupture of alveoli near the hilus of the lung. In a case of extreme subcutaneous emphysema complicating the pneumonia of influenza, the writer was able to detect a small, transverse, slit-like tear of the mucosa of the main bronchus of the right lung, a steady stream of bubbles escaping from this lesion when the lungs were inflated under water. Meyer and Lucke, in a recent discussion of subcutaneous emphysema as a complication of influenza pneumonia, describe necrosis of the smaller bronchi as the lesion which permits the escape of air, the latter travelling in the peribronchial tissue to the hilus of the lung. Whatever may be the lesion of the lung which leads to the escape of air, and wherever it may be situated, in cases of the kind under consideration the air reaches the mediastinum, from which it escapes to the tissues of the neck by the incisura jugularis. In the neck the air follows the fascial planes and may finally reach a wide-spread distribution in the subcutaneous tissues of the face, arms, and trunk. The lower extremities usually remain free. In such cases the path of the air is at first central or centripetal.

In another group of cases the path of the air is centrifugal, *i.e.*, away from the hilus of the lung. Gittings has reported three cases of subcutaneous emphysema following exploratory punctures of the chest in children. For this to occur the lung must be adherent to the chest

wall, in order that the air may escape from the lung along the needle path into the subcutaneous tissues of the chest. A similar condition may result when an adherent lung is torn by fractured ribs.

Subcutaneous emphysema is not a condition which arises spontaneously in a normal individual, but is a complication of some other process. In children it is most frequent in the bronchopneumonias of measles, whooping-cough and scarlatina, and in tuberculosis. In these diseases the increased intrapulmonary pressure of an attack of coughing may be the immediate factor which causes rupture of dilated alveoli or of air-spaces and bronchi weakened by inflammation. In some cases, coughing does not appear to be a factor. In these the air pressure may be increased by partial obstruction of bronchioles by exudate, or the walls of alveoli or bronchi may be so weakened by the inflammatory process present that the normal pressure is sufficient to cause rupture. The normal lung tissue of asphyxiated newborn infants may be torn by resuscitation procedures, as in the case reported by Wilkins. Faber has recently reported a case in an infant of three days, in which the condition was apparently due to partial asphyxia. He refers also to two cases reported by Guillot in 1853, one in a girl 10 days old, the other in a girl six days old.

The diagnosis of subcutaneous emphysema is easy and is established by the crepitation present in the tissues. The marked edema of nephritis in children may lead to appearances like those of subcutaneous emphysema, but in the latter condition the lower extremities are usually not swollen, and the swelling present is due to air and not to fluid. Cyanosis and dyspnea may be extreme. The prognosis is that of the underlying condition. If the latter is overcome, the air in the tissues is absorbed in from one to two weeks. The only treatment which can be of any avail is that which is directed toward quieting the respiration, thus helping to prevent the continuous escape of air into the tissues. Puncture of the skin, for the purpose of permitting the air to escape, should not be done, because of the danger of introducing infection into the subcutaneous tissues, whose circulation and nutrition are interfered with by the air present.

MALFORMATIONS OF THE LUNG

Malformations, due to developmental errors, occur in the lungs as in other tissues and organs; in fact, minor abnormalities are not at all infrequent. All gradations occur, from such extreme ones as are incompatible with continued development or life, to such lesser ones as are not discoverable clinically and as have only slight importance anatomically. In between these extremes are some which the careful clinician must bear in mind and others which are of interest as possibilities of origin of thoracic tumors.

One of the earliest classifications of anomalies of the respiratory tract, that of Fürst, is still one of the best, because it includes the various possibilities. Advances in embryology have, of course,

invalidated some of Fürst's conceptions of the nature and origin of certain malformations. A detailed discussion of all the possibilities cataloged by Fürst would include much of little interest. It appears more advisable to consider only those malformations of the lung which are more frequently encountered or which may have some clinical or pathologic importance or interest.

Complete Absence of Both Lungs.—This condition is incompatible with life and is usually associated with other malformations of such an extreme grade that it has only teratologic interest. Schmit, however, has reported a case in which both lungs were absent in an eight months' stillborn fetus, which appeared normal externally. The lung anomaly was not associated with any other anomalies of note. A beginning had been made in the development of the respiratory tract, since the anterior portion of the esophagus for a distance of 18 mm. opened into a partial tube which contained incomplete tracheal cartilage rings. The incomplete trachea arose from a normal larynx above.

Congenital Absence of One Lung.—Failure of a lung to develop normally can apparently be due to abnormalities in the formation of the anlage of the lung, or to regressive changes in an anlage which had a normal beginning. Cases of the former type are usually reported as agenesis or aplasia of the lung; those of the second type as hypoplasia, primary atrophy, etc.

Agenesis of the Lung.—The lung may be represented by a minute mass of tissue which caps the end of a primary bronchus given off normally at the bifurcation of the trachea. When the bronchus is present it is usually smaller in diameter and shorter than that of the opposite normal side. In other cases no vestige of the missing lung is found and a bronchus is not given off to the side of the missing lung. The trachea, without bifurcation, may be continued directly into the bronchus of the normal lung. Or it may bifurcate, or even divide into three branches, the two or three primary bronchi thus formed going to the normal lung. Pulmonary vessels to the missing lung are absent, and the failure of the circulation to develop may be the primary factor in the causation of the lung anomaly. A single pulmonary artery runs from the right ventricle to the normal lung. The venous return from the normal lung may reach the left auricle by one or two vessels, or the vein may run to the vena azygos. The normal lung in most of the reported cases has been larger than normal. This enlargement is probably compensatory in those cases in which respiration is established. In a number of cases the lung present has shown abnormal lobation, and it is possible that this abnormality as well as size variation may be part of the same process which led to the absence of a lung. If any tissue is present as a rudiment of the lung it is covered by pleura and is composed of connective tissue which contains a few spaces lined by cuboidal epithelium. It may form a small nodule on the end of the bronchus, if the latter is present, or on the side of the trachea where the bronchus should have been given off. More rarely

the rudiment may be attached to the esophagus or may be found in the mediastinal tissue. In one-sided absence of a lung the thorax is normally formed; there is not the deformity of the chest which characterizes regression of the lung after birth. The pleural cavity on the side of the absent lung usually contains clear fluid.

Ellis, in 1917, tabulated 18 cases from the literature, and added one of a boy aged eight years. Still more recently Levy (1920) has reported a case in a man aged 49 years, and in his tabulation has included two cases not listed by Ellis. Eden's tabulation, made in 1904, included six cases not among those of either of the above writers. In the older literature Fürst found five cases other than those included above. Ponfick in 1870 reported a case as primary atrophy of the lung. Reinhold and v. Graff have each reported a case. Of the recorded 36 cases a few, especially those in which the vascular relationships were not determined or were not stated, may be doubtful examples of agenesis, and may be cases of regression. Of the 36 cases, six were in adults and six in still births. In 13 cases the right lung was absent, and in 23 the left. In none of the cases does the absence of the lung appear to have been an immediate factor of death. In addition to the vascular and respiratory anomalies which have been mentioned, other developmental errors were present in a few of the cases, such as diaphragmatic hernia, atresia ani, obliteration of the esophagus, and dermoid of the left eye with hypoplasia of the left side of the face.

The causation of agenesis of a lung has not been determined. Fürst considered the possibility of atavism, comparing the condition with that occurring normally in reptilia. Klebs explained the anomaly upon the basis of mechanical factors, *i.e.*, excessive rotation by the amnion of the caudal end of the embryo to the right and of the cephalic end to the left, causing excessive tension of the left side of the body below and of the right side above. In support of this he cited the greater frequency of left-sided absence of the kidney and of right-sided absence of the lung. In so far as this explanation is based on statistical grounds it cannot hold with reference to the lung, since in the majority of the cases now on record it is the left lung which is absent. The absence of the lung may be the result of a developmental error which is primary in the pulmonary vascular system. In the case of v. Graff and in one of Klebs' cases, misplacement of the lung anlage appears to have been the factor which caused the failure of development of the lung.

Although congenital absence of one lung is not incompatible with life and has gone unrecognized until autopsy, one would expect such physical findings as would make recognition during life easy, if the possibility of the rare condition is borne in mind. The clinical symptoms have been dyspnea and cyanosis. With signs and symptoms pointing to absence of a lung, symmetry of the chest is the important factor in helping to reach the conclusion that the condition had its origin before birth. The heart is usually displaced to the side of the absent lung. Some lung resonance may be obtained on the involved

side, due to the increased size of the lung present or to the presence of partial accessory lobes, as in Ellis' case.

Rudimentary Condition or Absence of an Entire Lung Due to Regression.—In a second group of cases of absent lung, the anatomical findings indicate that the lung was laid down normally, but that some later acting factor prevented further development or brought about regressive changes in the lung laid down. Ponfick's case of "primary atrophy," supposedly due to some intra-uterine inflammatory condition, has already been mentioned. Ratjen has reported a case which appears to be more certainly one of regression of a lung whose development was begun normally. The right lung was excessively large. The left bronchus was given off normally, but one inch below the bifurcation it was replaced by a fibrous strand 1½ in. long, which was continuous with a portion of bronchus ¼ in. long with a patent lumen. This portion of the bronchus ended in a small, airless, two-lobed left lung, which was supplied with a small pulmonary artery and vein. Here apparently there can be no doubt of the regression or failure of further development of a lung which had reached the formation of the normal two lobes, the condition apparently being the result of obliteration of the main bronchus. There may be some doubt as to the congenital nature of the condition, since the gross description makes mention of the presence of coal pigment in the rudimentary lung tissue. Ratjen concluded that the condition must have arisen during fetal life because the chest was symmetrical. In Oberwarth's case, the right lung was represented by a small, single-lobed structure, which contained bronchi, but these had no connection with the primary bronchus, which ended blindly. In Klebs' third case, the right lung was a small, flattened mass lying at the end of a rudimentary pulmonary artery and right bronchus.

It is impossible to draw a very sharp line of distinction between failure of development of a lung and primary agenesis on the one hand and between the first named condition and atelectasis of an entire lung with regression on the other. In true agenesis, absence of pulmonary vessels or complete absence of lung rudiment is an important differentiating characteristic. Clinically, absence of a lung due to regression during fetal life could not be distinguished from absence due to agenesis.

Hypoplasia of the Lung.—There are reported a few cases in which the lungs of stillborn fetuses were smaller than normal, and showed a deficient development of elastic tissue. Abnormal smallness of the lungs after respiration is established is probably due to partial atelectasis rather than to failure of the lungs to develop to normal size.

Abnormalities in the Position of the Lung.—In situs transversus of the thoracic organs the three-lobed lung is on the left side, the two-lobed one on the right. The relationships of the great vessels and of the trachea and esophagus are correspondingly altered. The condition is of no clinical significance. In failure of the thorax to close anteriorly, hernia of the lung may be associated with ectopia of the heart. In incomplete closure of the diaphragm, the lung may be displaced

from its normal situation and may be found wholly or partly in the abdominal cavity. Pressure exerted by the misplaced abdominal organs may play a part in the downward dislocation of the thoracic organs.

Excess Anomalies.—Here we may include an abnormal number of lobes, accessory lobes, and accessory lung.

Abnormal Number of Lobes.—Partial subdivision of one or more of the primary lung lobes by incomplete accessory fissures is not rare. Adami and Nichols mention the occurrence of abnormal lobation 71 times in 1500 autopsies at the Royal Victoria Hospital, 54 times on the right side, 11 times on the left, and six times on both sides. The lower right lobe is most often involved. In a stillborn, full-term fetus from the maternity service of the Michael Reese Hospital, the middle

FIG. 9.—Right lung still-born fetus. Division of middle lobe into three lobes.

lobe of the right lung was divided into three pyramidal lobes by two extra fissures which were given off from the normal fissure between the upper and middle lobes, and the lower right lobe showed an incomplete fissure. There were, therefore, five distinct lobes, with partial subdivision of the lower lobe. Such conditions are not true excess formations. The amount of lung tissue is not increased, but the increased number of lobes is due to abnormal duplicatures of the visceral pleura. The condition probably arises during the first month of intra-uterine life, since at the end of the first month the normal fissures are already laid down.

Accessory Lobes.—Having the appearance of a true accessory lobe, rather than that of a subdivision due to supernumerary fissures, is the condition in which a separate lobe lies at the upper part of the lung. Such accessory apical lobes are supplied by a branch from the bronchus of the upper lobe. The anomaly is most often due to a subdivision of the upper lobe by an abnormal course of the vena azygos, and then

occurs on the right side. In Adami and Nichol's series of autopsies this anomaly occurred six times. The genesis of accessory lobe formation has also been ascribed by Chiari to a division of the trachea into three primary bronchi by transposition of the eparterial branch of the bronchus to the trachea. The transposed bronchus remains small and supplies a superior accessory lobe. He described one case and collected 11 from the literature.

Accessory Lung.—Differing from the anomaly last considered is that in which a small mass of lung tissue is situated at the base of the lung and has no connection with the normal lung or with the bronchial

FIG. 10.—Right lung. Child one year old. Incomplete separation of upper and middle lobes.

system. While of no clinical significance the condition is of embryologic interest and has been the cause of considerable investigation and some controversy. Bert and Fischer reported a case and collected and analyzed 12 others from the literature. In every case except one the structure was on the left side. It lies usually at the level of the tenth thoracic vertebra, between the base of the left lung and the diaphragm, and is covered by the diaphragmatic pleura. It is small, the maximum diameter being usually 4 cm. It contains rudimentary bronchi, which have no connection with the normal bronchial tree. Rudimentary lung alveoli are also present. The arterial supply is usually direct from the aorta, and in most cases the venous return is

to one of the azygos veins. In four cases the mass of accessory lung tissue was abdominal, being situated high under the diaphragm close to the tenth dorsal vertebra.

The origin of the anomaly has been a matter of dispute. Beneke considered the condition the result of abnormal division of the bronchial tree, just as Chiari held the accessory apical lobes to be due to abnormal branching of the trachea. Eppinger, however, with whom Bert and Fischer agree, believed that the formation of such accessory masses of lung tissue is due to displacement caudalward of part of the primary respiratory anlage in the foregut. According to this conception the accessory structure would never at any time have had any connection with the normal respiratory tract. Bert and Fischer hold that the occurrence of paraesophageal cysts lined by ciliated cylindrical epithelium, like those reported by Kern and by Stilling, support this view. These, and even ciliated cysts of the liver, of which Zahn reported 11 cases, are held to be evidence that the potentiality of the foregut to form respiratory tissue is not limited to the restricted area which gives rise to the normal respiratory tract. Aside from its embryologic interest, misplacement of respiratory tissue is important as a possible source of origin of thoracic tumors.

Failure of Formation of Normal Number of Lobes.—This is one of the more frequent anomalies, and like the formation of an extra number of lobes through supernumerary fissures, is of little practical importance. It is due to a failure of the normal pleural duplicatures to be formed. The condition may be bilateral and complete, both lungs being single lobed. Usually only some one or other fissure is incompletely formed, so that the right lung may have only two lobes, or the left only a single lobe.

Atelectasis.—A collapsed, airless condition of the lung is the normal state of the lung during intra-uterine life. With the establishment of respiration, the tissue becomes expanded. During the first few days of life the respiratory exchange is small and the respiratory center is said to be less sensitive to stimulation by carbon dioxid than later. Expansion of the lungs, therefore, occurs gradually over a period of days, and not suddenly with the first breath. If for any reason the normal expansion of the lung is interfered with at birth, then the persistence of the fetal, airless condition may be termed congenital atelectasis, in contradistinction to the acquired form, in which expansion occurred but the air is later absorbed. Congenital atelectasis may be due to occlusion of bronchi by developmental defects, perhaps by intra-uterine inflammation, or by mucus. Intra-uterine inflammation of the pleura, with adhesions which interfere with expansion at birth, has also been given as a cause of atelectasis. Respiration may be incompletely established through weakness of the child, or through pressure upon the respiratory center by hemorrhage. If the involvement is sufficiently widespread, the atelectasis is incompatible with life. When due to a general condition, such as weakness of, or pressure upon, the respiratory center, the posterior portions of the lungs

are involved, because the excursion normally is least here, or the involvement may be at the center of the lung near the hilus, because of the angle at which the bronchi are given off. When due to bronchial occlusion, that portion of the lung supplied by the occluded bronchus fails to expand. If the failure of expansion is not obstructive in nature the atelectasis is not complete at first, as has been shown by Peiser.

The further changes which the atelectatic lung may undergo are variable. The first changes to occur are stasis of blood with hemorrhage and edema of the air-spaces. Later the alveolar epithelium degenerates and the septal tissue proliferates. In the course of time the interstitial tissue shrinks, and the affected portion of lung may show only bronchi and blood vessels embedded in dense stroma, which may contain scattered areas recognizable as remnants of alveoli. When seen early, atelectatic areas are bluish red in color, shrunken, and have a leathery consistency. After a longer time the tissue is pale and stands out sharply from the normal lung by its decreased area and by its absence of pigment. In some cases the atrophy and shrinkage of interstitial tissue seem to exert an outward pull upon the bronchi, leading to dilatation of the latter, the resulting condition being known as atelectatic bronchiectasis. Although, according to some, bronchiectasis always follows as an end stage of atelectasis, Olga Lotmar and others have shown that dilatation of the bronchi need not occur as an inevitable result of the interstitial indurative process.

Fetal Bronchiectasis.—Three types of fetal bronchiectasis are recognized: Atelectatic bronchiectasis, telangiectatic bronchiectasis, and universal bronchiectasis.

Atelectatic Bronchiectasis.—In this form, distended bronchi are scattered about in a dense, airless, non-pigmented tissue. If the bronchial dilatation is due to external traction upon the bronchi by the shrinkage of the interstitial atelectatic tissue, then the bronchiectasis is secondary to atelectasis and is not a primary developmental anomaly. If the atelectasis is not due to bronchial obstruction, air pressure within the bronchi may also be a factor in causing dilatation of the bronchi. Inflammatory processes are usually present in the walls of the latter, so that weakening of the walls would aid in bringing about dilatation. But these mechanical factors do not seem to be the only ones concerned in the causation of the dilatation in some cases, and in these the bronchiectasis may be primary and congenital and not secondary. The walls of the dilated bronchi may be greatly hypertrophied and the amount of cartilage may be increased. Such changes Heller interpreted as due to continuation of growth in the bronchi, while atrophic changes were occurring in the interstitial tissue. Buchmann and others have described the presence of large amounts of smooth muscle in the interstitial tissue, together with marked hypertrophy of the muscle of the blood vessels and bronchi. The amount of smooth muscle may be so great as to give the tissue the appearance of a leiomyoma. Because of the overgrowth of muscle and cartilage

which occurs in some cases, Buchmann holds that atelectatic bronchiectasis may be a primary developmental anomaly, characterized by hypertrophy of bronchi, smooth muscle, and cartilage, and by failure of the alveolar lung tissue to develop. Arnheim has reported a case of complete hemiatrophy of the body with atelectatic bronchiectasis of the lung of the opposite side, a combination which he thinks favors the developmental nature of the condition. This conception is the one, also, which Ziegler favors. The clinical manifestations are those of acquired bronchiectasis.

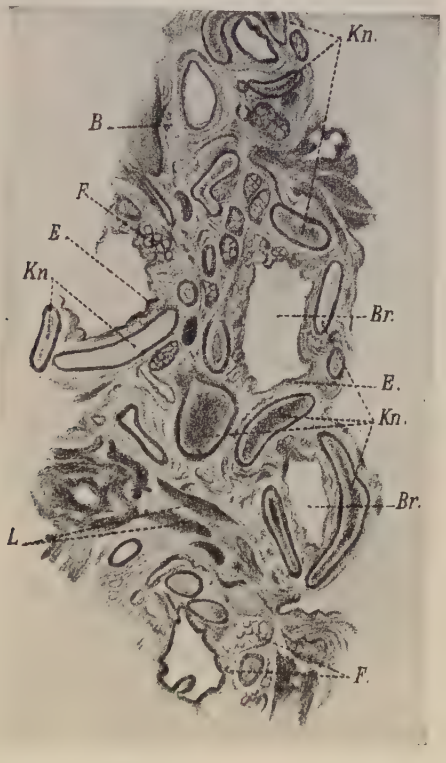

FIG. 11.—Fetal bronchiectasis. *B*, fibrous tissue; *Br*, hypertrophied, dilated bronchi; *E*, epithelial lining of bronchi; *Kn*, bronchial cartilage; *F*, peribronchial adipose tissue. × 6. (After Arnheim.)

Telangiectatic Bronchiectasis.—In this condition cyst-like areas from a few millimeters to 1 cm. or over in diameter are present in some restricted portion of the lung, or they may be scattered diffusely throughout both lungs. In the gross the appearance may be very suggestive of a marked bullous emphysema. Edens collected 13 cases from the literature. One case from the Michael Reese Hospital has been reported by Abt and Straus as a case of emphysema with bronchiectasis. Re-examination of the sections by the writer leads to the conclusion that the case was one of telangiectatic bronchiectasis with

which emphysema was associated. In this case both lungs in a boy of 12 years were diffusely involved. Microscopic examination shows the cysts to be formed by rounded dilatations occurring in the course of the smaller bronchi. The smaller cysts are lined by bronchial epithelium. In some of the larger ones the lining epithelium is replaced by a thin layer of inflammatory material composed largely of lymphocytes. In others there is a thick layer of rather large, polygonal cells, which in places can be traced to proliferation of the bronchial epithelium. In some areas cells of this type are present in large numbers in the tissue about some of the cysts. Marked bronchial epithelial hyperplasia, such as this case shows in places, led Störk to consider the possibility that some cases of fetal bronchiectasis might be examples of

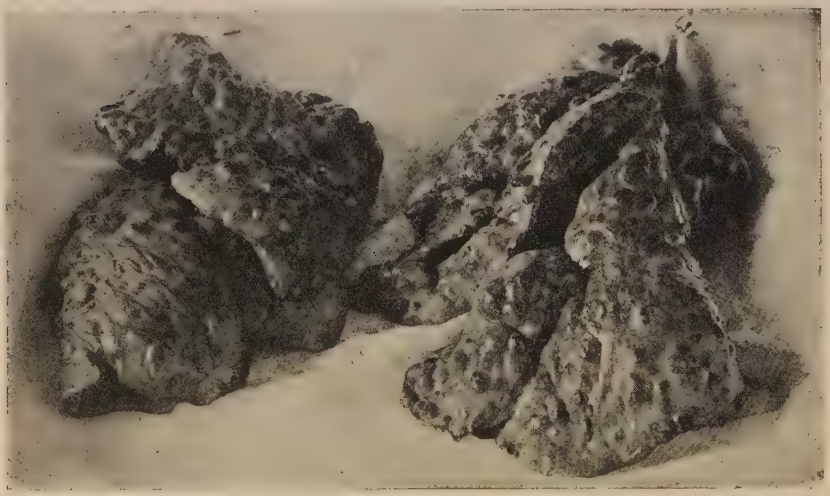

FIG. 12.—Lungs showing multiple cysts of telangiectatic bronchiectasis.

fetal adenoma of the lung. No cartilage is present in the walls of the cysts, and the amount of muscle is small, indicating that the cysts have been derived from smaller bronchioles. Continuation of cysts into infundibula can be seen. The lung tissue between the cysts is emphysematous in places. Immediately about some of the cysts it is somewhat compressed. In this case spontaneous pneumothorax occurred as the result of rupture of one of the subpleural cysts.

In telangiectatic bronchiectasis the dilatations are saccular and occur usually in the course of the bronchioles. The cyst-like cavities are in communication with the respiratory system through the bronchial tree on the one hand, and often with the infundibula and air-sacs on the other. Compensatory emphysema occurs in the functional lung tissue between the cysts. The walls of the latter may be the seat of inflammatory processes, which may spread to the surrounding lung tissue. The clinical manifestations are those of emphysema, and of bronchiectasis when inflammation is present.

Universal Bronchiectasis.—Meyer, who described two cases of this anomaly in 1859, stated that he was unable to find a record of a similar condition in the previous modern literature, but noted that descriptions of apparently the same condition occur in the works of Malpighii and other early writers. In his first case, attacks of cyanosis and asphyxia began in the fifth month of life, death occurring in such an attack at the age of one year. The upper lobe of the left lung was

FIG. 13.—Gross photograph of thoracic and abdominal viscera, showing large size of lung cyst. (Koechert in Amer. Jour. of Dis. of Children.)

transformed into an air filled sac, 11.1 by 9.3 cm., which communicated with a bronchus. In the second case, a stillborn fetus of the fifth or sixth month, the greater portion of the right upper lobe was transformed into a fluid-filled cyst, and the remaining portions of the right lung, as well as all of the left lung, contained numerous small cysts, which were continuous with the bronchi. This was quite evidently a combination of telangiectatic and universal bronchiectasis. Grawitz, in a discussion of congenital bronchiectasis which included four cases of the telangiectatic form, described also two cases of the universal type.

In his first case, a cyst of the right lower lobe of a stillborn, full-term fetus, the bronchus running to the cyst was occluded. Grawitz established the bronchial origin of these large lung cysts by showing that they are lined by cylindrical ciliated epithelium. The fibrous wall of the cyst may contain compressed, undeveloped lung alveoli. Grawitz' second case, a man who died at the age of 25 years after marked cyanosis and dyspnea, is extremely interesting, because like Meyer's case in the stillborn fetus, it appears to be an example of combination of telangiectatic and universal bronchiectasis. A large cyst occupied most of the lower right lobe, whereas the small portion of the lower lobe not included in the large cyst and all of the tissue of the middle and upper lobes of the right lung was honeycombed by small cysts. Koeckert has described the most recent case. The child was moderately cyanotic at birth. Dyspnea and cyanosis increased and death occurred one and one-half hours after birth. The upper left lobe was transformed into a large cyst, over the wall of which compressed lung tissue was spread out. The lower left lobe was atelectatic. No communication with a bronchus could be established, but the cyst wall contained cartilage and smooth muscle and was partly lined by bronchial epithelium. The cyst contained a small amount of air (it is difficult to understand the presence of air in the absence of an open bronchial connection) and 75 c.c. of fluid, which chemically was very similar to amniotic fluid.

Universal bronchiectasis is characterized by the presence of a single large cyst, which occupies most of a lobe. The inner surface of the wall may show falciform bands, derived apparently from the walls of smaller cysts which have been incorporated into the main cyst. In two cases multiple small cysts of telangiectatic bronchiectasis throughout the lung were associated with a large cyst. Grawitz' designation of bronchiectasis universalis for the large cyst variety does not appear entirely appropriate, since it suggests dilatation of the entire bronchial tree. He believed the large cyst to result from dilatation of a main bronchus and all its branches, and the term is a proper one only if it is understood that "universal" relates to a main bronchus and its branches and not to the bronchial tree as a whole. In the telangiectatic variety, characterized by the presence of multiple small cysts, the latter have multiple, often widely separated, points of origin in the smaller bronchi.

No theory which gives a satisfactory explanation of the origin of the three kinds of fetal bronchiectasis has been proposed. That the telangiectatic and universal forms may be present in intra-uterine life is established, hence they must be considered to have their origin in developmental disturbances. That atelectatic bronchiectasis is considered by some to be a developmental anomaly, rather than a condition which is acquired secondary to congenital atelectasis, has already been mentioned. But what the underlying factor or factors may be in initiating the error has not been established. Virchow, in describing what apparently was a case of telangiectatic bronchiectasis in a still-

born cretin, considered the cysts to be formed from dilated lymphatics and compared the lung condition with congenital macroglossia. Grawitz compared the telangiectatic form with congenital cystic kidney, and explained the universal form as a hydropic dilatation of a main bronchus and its branches. Kimla, in explanation of cystic degeneration of glandular organs in general, supposed a relative overgrowth of the mesodermal tissue at an early stage of fetal development, the glandular elements then undergoing either atrophy or hyperplastic changes as the result of the altered conditions to which they are subjected. For cases of bronchiectasis of the cystic type, he supposed that the development of the bronchial system ceases at the third to fifth month, the bronchi becoming dilated as the result of epithelial proliferation. For atelectatic bronchiectasis he also postulated cessation of development of the bronchial system, with dilatation of the bronchi by epithelial proliferation, this process being associated with hyperplasia of the elements of mesodermal origin. Couvelaire considered proliferation of the epithelial elements the primary and essential factor. Intra-uterine inflammation with bronchial obstruction followed by dilatation due to retention of secretion has also been held to be a possible cause of fetal bronchiectasis. The association of the telangiectatic form of bronchiectasis with the large cyst, universal form, in two of six reported cases, indicates that there may be a common factor in the origin of at least these two types.

TUMORS AND CYSTS OF THE LUNG

The lung is one of the relatively infrequent sites of primary malignant tumor involvement in adults, the incidence of primary carcinoma being about 1 per cent. of cancer autopsies (Ewing). In children the relative frequency appears to be even less. Ewing refers to two cases, one in an infant of five and one half months, the other in a girl seven years. These were reported in the years 1875 and 1876 and must be considered doubtful. Ribbert doubts the occurrence of primary carcinoma of the lung in children and questions the correctness of the diagnosis in the very few cases reported. Toward primary sarcomata of the lung Ewing takes a sceptical attitude and concludes that "only a minority of the reports present sufficient evidence to justify their separation from diffuse carcinoma." He refers, in passing, to four cases in children: A diffuse spindle-cell sarcoma in a child, and three round-cell sarcomas, one at two years, one at three years, and one at five years. Ribbert was able to collect four cases: A spindle-cell sarcoma 10 cm. in diameter in the right upper lobe of a girl of 14 years; multiple soft tumors filling the left thorax in a boy of three and one half years; a round- and spindle-cell sarcoma of the left lung of a girl of 11 years; and a medullary sarcoma of the right upper lobe in a girl of 13 years, the tumor being the size of a child's head. Lehndorff, whose case is included by both Ewing and Ribbert, furnished no microscopic description of his tumor; it arose from the tip of the left lower lobe and was encapsulated. A partly calcified fibroma, which

replaced the upper and middle lobes of the right lung of a girl of 13 years, is credited by Ribbert to Przewowski. Parkinson has reported a case of primary sarcoma of the lung in a child, and Hall and Tribe a case of carcinoma of the bronchus and liver associated with glycosuria.

There are in the literature a few other tumors of the lung in children which are of general interest because they belong to the group of tumors which are to be considered embryonic maldevelopments. Linser has reported a case of congenital adenoma of the left lung in a boy of 13 years. The tumor had caused pain in the left chest, dulness on percussion, skoliosis, dyspnea, and dislocation of the heart to the right. It measured 20 by 9 by 11 cm. The atelectatic left lung lay behind and below the tumor mass. The latter was composed of branching canals lined by non-ciliated cylindrical epithelium, and of gland-like and cystic spaces lined by several layers of polyhedral epithelium. Because of the character of the epithelial constituents of the tumor, Linser concluded that it must have arisen early in embryonic life. A tumor which contained similar epithelial elements and which had replaced all of the left lung except a small area at the hilus, in a still-born fetus of the eighth month, has been described by Zipkin as an adenorhabdomyoma. This tumor was more complicated in structure, in that striated muscle tissue was present throughout it. Smooth muscle was absent, being replaced by striated muscle even in the walls of the small number of bronchi present. The embryonic bronchioles were lined by ciliated epithelium. Elastic tissue was absent in the walls of the blood vessels. Zipkin concluded that the striped muscle was derived from misplaced myotomes, and suggested that the displacement of the muscle tissue into the lung anlage may have been the primary factor, the adenomatous proliferation of lung elements being secondary to the growth of the muscle tissue. The case reported by Muus is of great interest because the tumor developed in an accessory lung. It occurred in a full-term male infant, which died 24 hours after birth. Cyanosis had increased progresssively from birth. The tumor was a polypoid mass, the size of a walnut, which lay in a depression in the base of the lower lobe of the left lung, to which it was nowhere attached. It was covered by diaphragmatic pleura. A narrow pedicle extended through the diaphragm to the wall of the stomach. The pedicle contained a short narrow canal, which was not continuous with the gastric mucosa. The wall was formed of cylindrical epithelium, smooth muscle and cartilage. The mass itself contained gland-like alveoli lined by a single layer of ciliated cylindrical epithelium, present in such amounts that the structure was considered adenomatous. In the septa were smooth muscle, elastic tissue and striated muscle. The last-named constituent Muus believed to have been derived by metaplasia, but admitted a second possibility of derivation from the muscle of the diaphragm. He explained the origin of the mass as due to splitting off from the original lung anlage, with displacement posteriorly by the growth of the intestinal tract. The case appears to uphold the view of Eppinger, and of Bert and Fischer, that such

accessory lung structures are due to independent origin of a bud of respiratory tissue from the primitive foregut at a point posterior to the normal respiratory area. Helbing has reported a rhabdomyoma which had replaced the left lung is a man dying at the age of 23 years. The tumor contained scattered islands of cartilage and little epithelial tissue. The striated muscle was not uniformly distributed. This tumor differs from Zipkin's in that the lung tissue took no part in the proliferative process. A papillary cystadenoma reported by Björnsten, in which the lung contained multiple small cysts lined by cylindrical epithelium which formed papillary ingrowths, appears to be a case of congenital telangiectatic bronchiectasis, in which hyperplasia of the bronchial epithelium is not unusual. A case of multiple gliomatous nodules in the lungs of an anencephalic monster dying one-half hour after birth, reported by Askanazy, is interpreted by Ribbert as the result of displacement into the lungs of glia tissue from the malformed brain.

Primary tumors of the pleura in children belong among the pathological curiosities. Hofmokl reported a small round-cell sarcoma of the pleura in a child of three and one-half years, the tumor forming multiple nodules of varying size. The same writer also described as an endothelial sarcoma a large-celled, alveolar tumor of the right pleura in a boy of seven years. This tumor, like the alveolar one reported by v. Hibler in a boy of five and one-half years, apparently belongs to the group of tumors derived either from the lymph-vessel endothelium of the pleura or from the surface endothelium of the membrane, tumors which are placed by some among the endotheliomas and by others among the carcinomas. According to v. Hibler, Glockner, in a collection of 75 cases of endothelial tumors of the pleura from the literature, was able to find eight cases in which the tumor arose in childhood. V. Dieballa and Entz have reported a case of spindle-cell sarcoma of the right pleura in a girl of 15 years, in whom cough, dyspnea and cyanosis has been present for six years. In this case there was leukocytosis of 112,600, with 82.8 per cent. polymorphonuclear cells and 10 per cent. myelocytes. Since there were only four small bone-marrow metastases, the leucocytosis was ascribed to the action of toxic products derived from the tumor. The clinical manifestations of tumor of the pleura are those of chronic pleuritis. The fluid is apt to be bloody, is replaced quickly after removal, and may contain free tumor cells. Subcutaneous nodules may develop in the line of puncture made by the needle in thoracocentesis. The side of the chest may be retracted.

The occurrence of secondary tumors of the lungs in children is dependent upon the incidence of metastasizing tumors at this early period of life. Metastatic tumors of the lungs will, therefore, most often be sarcomas. The mixed embryonal tumor of the kidney, one of the tumors peculiar to the early years of life, may metastasize to the lungs: the secondary tumors are usually sarcomatous in type although the presence of striated muscle has been noted. Lehndorff, under the title "bronchitis chloromatosa," has reported two cases of

chloroma in which the lungs showed multiple peribronchial chloromatous nodules, which were believed to have developed by retrograde growth along the peribronchial lymph channels from the involved hilus nodes. The bronchi were filled with tumor cells, which gave to the sputum during life a greenish color.

Epidermal Inclusions of the Lung.—Fürst collected from the older literature three cases of dermoid of the lung. All were in young women of the third decade of life. In each case there was chronic cough, with other symptoms like those of pulmonary tuberculosis. The sputum contained hairs like those found later at autopsy in the dermoid. The tumors arose primarily from the pleura or the mediastinal tissue. A number of mediastinal dermoids and teratomata have been reported in more recent years, but need not be considered further at this time.

Cysts of the Lung.—Cysts of the lung, as reported in the literature, appear to be examples of congenital bronchiectasis, which has been considered above. The occurrence of cysts, in the mediastinum and even in the liver, derived from misplaced respiratory system tissue, has been discussed under accessory lung formation. Cyst formation as a part of hydatid disease of the lung has been considered under echinococcus of the lung.

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CHAPTER LXVI

SURGERY OF THE THORAX

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MALFORMATIONS OF THE THORAX

The malformations of the thorax for the most part are of little surgical interest at present. They concern not only the thoracic wall but also the thoracic contents. In those of the thoracic wall both the bones and the soft tissues are concerned. Of the bony malformations, median fissure of the sternum is one of the most frequent. This may

Fig. 14.—Congenital defect of right pectoralis major muscle. Note the absence of hair on the side of the chest affected. (From Washington University Dispensary.)

be so pronounced that the two halves of the sternum separate and approach with each respiration. H. Fischer[1] described a case in which at the end of inspiration the split in the manubrium was 6 cm. wide, at the end of expiration 4 cm. wide. When such complete fissures exist the space between the two halves is usually occupied by fibrous tissue. The fissure may not be complete but may involve only one end of the sternum. The condition does not ordinarily call for surgical treatment; but if in the exceptional case it should seem necessary, an operation for uniting the two halves might be carried out. Lannelonge[2] has

reported a very dramatic case of sternal fissure in a girl 14 years old the ventricles of whose heart were entirely exposed because of ulceration of the skin. A plastic operation was performed and when seen eight years later she was well and the mother of two children.

Malformations of the ribs occur of many different kinds, abnormal numbers, abnormal attachments (especially to the sternum) and abnormal fusions to each other.

Congenital defects of the muscles have been observed in a considerable number of cases. Stintzing[3] in 1886 collected from the literature 13 cases in which the pectoralis major muscle was lacking. (Fig. 14.)

Abnormal defects in the chest wall occasionally give rise to hernia of the lung. These hernias are usually not congenital but make their appearance during infancy. Kümmell[4] quotes Buntzen as having seen a hernia of the lung in a girl which appeared when she was 14 days old. It disappeared spontaneously. Bieser,[5] however, has reported a case of apparently undoubted congenital hernia which appeared in the right supraclavicular fossa as soon as the child began to breathe. It was easily reducible but did not stay reduced. Death, apparently from asphyxia, occurred two days after birth. An extensive discussion of the subject of congenital lung hernia may be found in Hochsinger's[6] article. These hernias have a sponge-like consistency and may crepitate. They become larger on expiration and have a distinct impulse on coughing. Operative repair is usually not necessary, since, as a rule, the application of a snugly fitting pad is sufficient. Acquired hernias of the lung will be discussed elsewhere under "Penetrating Injuries of the Thorax."

INJURIES OF THE THORAX

Non-penetrating Injuries

Contusions.—As a result of sudden force applied to the chest wall the structures within the thorax may often be extensively injured even although external evidences of injury are slight or absent. This is particularly true of young children, in whom extreme compression of the thorax can be made without fracture. It is possible to show in the infant cadaver that the sternum can be pushed back practically to the spine without fracture of either the ribs or sternum. As soon as the pressure is released the thorax assumes its normal shape because of the elasticity of its walls which in children is especially marked. As might be expected, the more serious consequences follow the application of sudden rather than gradual force. This is due chiefly to the fact that in the sudden injuries there is less opportunity for the escape of air from the lungs through the trachea, with the result that not only are the inflated lungs more likely to be bursted by the force but also the failure of the lungs to diminish in size in turn probably increases the risk of injury to the other thoracic organs. It is very important, particularly for the general practitioner, to recognize the fact that injuries which may be severe enough even to have fatal consequences may be produced in accidents which leave little or no external evidence.

Common causes of injury unassociated with fracture are accidents, in which the child is run over by a vehicle, falls from considerable heights, or is jammed between heavy bodies. The pathology of such injuries may be most complex because of the multiplicity of lesions of the intrathoracic organs. The lungs, the heart, the great vessels, the diaphragm, the trachea and the esophagus may all be affected. Not uncommon also is the involvement of the abdominal viscera, especially the liver, spleen and kidneys. On the other hand, it is often surprising to find that a child has completely escaped serious injury in spite of having been run over by a heavy vehicle. The writer has seen two young children, one of whom was run over across the thorax by

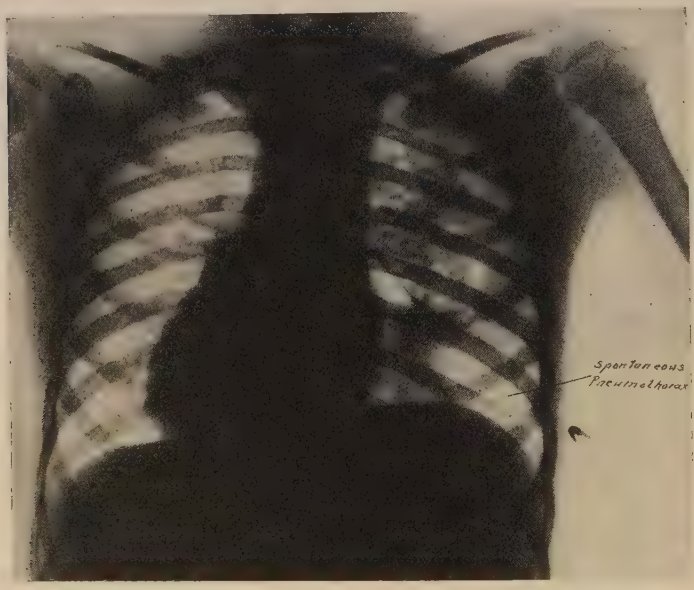


FIG. 15.—Pneumothorax resulting from a crushing injury of the chest without fracture of the ribs. (From St. Louis Children's Hospital.)

two wheels of an automobile, and the other by one wheel, without any serious consequences except for a little blood-tinged sputum in the case of the former. McDonnell[7] has reported the case of a young man, aged 24, whose chest was run over by a heavy cart wheel. Death occurred 10 days later, and at the necropsy there was no evidence of fracture of any of the ribs or of the sternum despite the fact that the left lung was extensively lacerated and that the left pleural cavity contained 3 qt. of blood in addition to gas. At the same meeting of the Dublin Pathological Society Lyons reported a case of laceration of the lungs without fracture of ribs and Smith was quoted as having seen four other cases. More recently cases have been reported also by J. Ashhurst, Jr.,[8] and others. Quénu[9] has reported a case of injury of the lung without visible injury to the skin. In the accompanying illustration (Fig. 15) is shown an *x*-ray picture of a pneumothorax resulting from

an injury to the chest without a fracture of the ribs in a child brought into the St. Louis Children's Hospital. This must have been due to a laceration of the lung as a result of the crushing injury.

Most often, however, injuries which are of sufficient grade to produce extensive lesions of the intrathoracic organs are accompanied by fracture of at least some of the ribs and frequently of the sternum as well.

Diagnosis.—The clinical picture is often very complex because of the multiplicity of lesions. As in all serious injuries, shock may be present and may even be extreme. Not uncommonly the picture of shock may not come on until an hour or more after the injury, an occurrence which should lead to a strong suspicion of extensive intrapleural hemorrhage. Intrathoracic hemorrhage in such cases is most often due to lacerations of the lung and less often to injuries of other intrathoracic structures. Hemoptysis usually follows a laceration of lung tissue, but yet rather extensive lacerations without hemoptysis have been noted. The usual signs of pleural effusion may be made out and exploratory aspiration will establish the diagnosis of hemothorax. It is most important of course to recognize that fatal hemorrhage may take place within the thorax just as within the abdomen.

Pneumothorax may be present alone if the trachea or a large bronchus has been injured, or in association with a hemothorax. If it is of a valvular variety which permits the entrance of air into the pleural space but prevents its exit it may produce alarming symptoms of extreme dyspnea and cyanosis.

Emphysema of the chest wall has been reported even after injuries unassociated with fracture of ribs. If emphysema of the wall occurs, however, a fracture of ribs should be suspected. Mediastinal emphysema also occurs and is usually a very dangerous complication. The characteristic sensation of crepitation makes the diagnosis of subcutaneous emphysema easy.

Laceration of the diaphragm occurs occasionally with a resulting displacement of some of the abdominal organs into the thorax. It is remarkable that occasionally practically no symptoms may be produced by this displacement and the condition may not be recognized until years after the injury and then only by accident. Riedinger and Kümmell[10] mention a case of their own in which the stomach, part of the colon and the liver were dislocated but yet the condition was not recognized until necropsy many years later. Hernia of the lung has been reported without an associated fracture of the ribs. It so frequently happens that the abdomen is injured at the same time as the thorax that the clinical picture is still further complicated by the multiplicity of the abdominal lesions.

After the disappearance of the initial state of shock various secondary symptoms may appear, and the clinical picture may change completely. A pneumothorax may have completely disappeared within a few days. The pleural effusion may have become larger,

not so much because of more hemorrhage as because of an infection of the extravasated blood with a resultant empyema. This latter condition, however, is much less common in non-penetrating injuries than might be supposed when one considers how extensive the lacerations in the lung often are and the ease with which bacteria can find their way from the upper air-passage to the extravasated blood. Pneumonia, however, is common. In a patient under the writer's care who had received a severe non-penetrating crushing injury of the right side of the thorax with the fracture of five ribs, there was practically no hemothorax but a large hematoma in the chest wall. Death occurred three days after the injury from fat embolism, the diagnosis of which was made clinically and confirmed by microscopic examinations of the lungs and brain.

Another curious complication of thoracic injuries is the phenomenon of massive collapse of the lungs. Attention was first directed to this condition by W. Pasteur[11] and since his article several contributions have been made to the subject chiefly by the British. A summary of the present knowledge of the subject is contained in a recent article by Bradford.[12] In this condition a considerable portion of one lung or a whole lung becomes airless and on physical examination often gives signs of pulmonary consolidation. An important point of differentiation, however, is that the diaphragm on the affected side is high and seems fixed. It occurs more commonly in association with penetrating than with non-penetrating wounds of the chest. It is frequently contralateral and may even occur after injuries to other parts of the body, notably the abdomen. The condition seldom lasts for more than a few days.

Prognosis.—Injuries to the chest associated with lesions of the intrathoracic organs are always serious, and the mortality is high. Schwartz and Dreyfus[13] have reported a series of 29 cases of laceration of the lung without fracture of ribs, death occurring in 16.

Treatment.—In mild cases of contusion no special treatment is necessary. In the more severe cases and especially if there is any suspicion of injury to organs, the patient should be put at absolute rest. If shock is present it must be energetically treated by external heat and the copious administration of fluid. Since in many of these cases the shock is a result of hemorrhage, blood transfusion should be carried out.

In cases of large hemothorax aspiration will often relieve the dyspnea materially and will probably also diminish somewhat the risk of pyothorax from infection of the extravasated blood. In extensive acute pneumothorax, especially of the valvular variety, repeated aspiration of the air may be necessary to save life from asphyxia. Hematomas of the chest wall should be aspirated. If fractures of the ribs are present strapping or other methods of immobilization will often give relief; yet sometimes such methods seem to aggravate the discomfort. If alarming hemorrhage persists an effort should be made to control it by open operation of a sort so frequently employed

in the Great War. Lacerations of the diaphragm will usually require suture, preferably in most cases through the thorax. If pyothorax supervenes it should be treated in accordance with the general principles discussed in a later section on "Empyema."

Other Non-penetrating Injuries.—Other non-penetrating injuries may be produced by burns, projectiles, explosions, cuts from knives, glass, etc. They do not require extensive mention here because they do not differ essentially from injuries of the same character in other parts of the body. It is sometimes difficult to be sure that a wound is limited to the thoracic wall and has not penetrated. For that reason it is of the greatest importance to search for evidence of injury to contained viscera even in cases which are apparently limited to the chest wall; and the possibility of injury to the lung should always be borne in mind. Examination with the *x*-ray for pneumothorax, pleural effusion, etc., should always be made. The prognosis of injuries limited to the chest wall is generally good, and the treatment does not differ materially from that of the same type of wounds in any part of the body. Hemorrhage is occasionally severe but usually is slight.

Penetrating Wounds of the Chest

Penetrating wounds of the chest are most commonly produced by projectiles and by cutting instruments such as knives, daggers, etc. For obvious reasons they are much less common in children than in adults. The serious nature of penetrating wounds is due chiefly to the resultant hemorrhage, infection and pneumothorax. The whole picture may be better understood, therefore, if some space is devoted to a consideration of these three associated phenomena.

Hemorrhage is the most common complication. Every penetrating wound is accompanied by some hemorrhage which may be slight or severe depending of course upon what structures have been involved in the injury. The lung is sometimes traversed by a small projectile, as a rifle or revolver bullet, with relatively little hemorrhage. On the other hand, if the heart, the large vessels, the liver, or the spleen have been injured extensive bleeding almost always occurs. The serious effects of intrathoracic hemorrhage are due not only to the acute anemia produced but also to pressure effects upon the thoracic viscera. The diagnosis of intrathoracic hemorrhage is based upon the evident presence of shock, an acute anemia, the physical signs of pleural or pericardial effusion supplemented by the characteristic *x*-ray shadow and the aspiration of blood with an exploratory syringe. It is important to remember, however, that in addition to the free blood which may exist in the pleural cavity there is usually more or less extensive extravasation into the lung itself and there may also be severe hemorrhage into the abdominal cavity if a neighboring abdominal organ has been injured by penetration of the diaphragm. The amount of blood coughed up by the patient is a very unreliable guide on which to gauge the amount of hemorrhage which has occurred.

Extensive intrapleural hemorrhage may occur without any hemoptysis at all. It is rare to have copious hemorrhage after a wound merely of an intercostal vessel.

Infection may occur not only as a result of organisms having been carried in with the missile but also through organisms which come from the respiratory tract itself. The extravasated blood and the injured tissue make suitable culture media for the growth of bacteria. Some degree of pneumonia, therefore, is common after all penetrating injuries of the lung. Pyothorax, however, is less common, and in many cases in which the lung has been traversed by a bullet of small caliber there is no recognizable pyothorax. Lung abscess is still less common and is associated usually with a foreign body retained in the lung, such as a fragment of clothing, a piece of rib, etc. A retained bullet less often gives rise to abscess formation than foreign bodies of other kinds. Gangrene of the lung is a complication which intensifies greatly the gravity of the prognosis. Gangrene produced by infections with some of the gas-producing bacilli is usually rapidly fatal.

Pneumothorax as a complication of penetrating injuries of the chest may be due to the presence of either air or gas from bacterial putrefaction. It is very rare to find it alone. Most usually the air or gas in a pleural cavity is associated also with blood or pus, in which case the condition becomes a pneumohemothorax or a pneumopyothorax. As a rule the mere accumulation of air or gas within the pleural cavity is not in itself of grave significance. In some cases, however, the amount of air may be so great that serious pressure effects will be produced. This is especially likely in cases of so-called valvular pneumothorax in which the air enters the pleural cavity with each inspiration but can not leave it again. The harmful effects of closed pneumothorax are due to altered pressure relationships within the thoracic cavity. An open pneumothorax in general is more serious than a closed one chiefly because of three reasons: (1) The respiratory difficulty is usually greater; (2) infection of the pleural cavity occurs probably in all cases; and (3) rapid loss of heat occurs. In general, the larger the wound the more serious is the condition. A detailed consideration of the physiology of pneumothorax will be given later in connection with the subject of Empyema.

Other complications of penetrating injuries of the chest arise depending upon what organs are injured. Thus, for example, injuries of the heart, the diaphragm, the thoracic duct, the esophagus, the spinal cord may occur which will complicate the clinical picture materially. Subcutaneous and mediastinal emphysema may also be present; and hernia of the lung sometimes occurs.

Symptoms and Diagnosis.—As might be supposed from the variable pathology accompanying penetrating injuries of the chest their clinical pictures are often complex. The symptoms depend largely upon what structures have been injured and also upon how much time has elapsed since the receipt of the injury. Soon after the injury the symptoms may be those chiefly of shock and later they may

be chiefly those of pleural and pulmonary suppuration. The presence of excessive amounts of air or fluid in the pleural cavity is manifested by the characteristic physical signs and is usually also accompanied by more or less severe dyspnea resulting from abnormal intrathoracic pressures. The presence of emphysema is easily recognized, if subcutaneous, by the characteristic crepitation. This may be very extensive and involve the entire side of the thorax and neck. Emphysema of the mediastinum usually produces extreme dyspnea. It may manifest itself by a crepitant swelling coming out of the thorax into the neck, by effacement of the cardiac dulness and the hearing of crackling sounds on auscultation. Associated fractures of ribs are common in this type of injury. Hernia of the lung is usually easily recognized. Injuries of the heart or pericardium are likely to be accompanied by precordial distress, acceleration of the pulse and marked dyspnea. *X*-ray examination of the chest is of the utmost importance in diagnosing not only the extent and the complications of intrathoracic injury, such as pneumothorax, the presence of fluid in the pleural cavity, diaphragmatic hernia, etc., but also the presence and location of any retained missile. Extensive progress was made during the war in the exact localization of missiles by the *x*-ray. For details of standard methods now in use reference should be made to some of the many articles and books which have appeared on military surgery. Ombredanne's[14] monograph will be found to be helpful.

The simple sterile hemothorax is usually associated with continuous fever which may occasionally be as high as 103°F. but which descends to normal within about a week. The patient generally feels and looks well, however, during this period after he has passed through the period of initial shock and dyspnea. If infection supervenes the symptoms are all aggravated. Complaint is made of pain in the chest, dyspnea is more marked, tachycardia is usually present, and the temperature assumes a septic type of curve. Cough is nearly always present and hemoptysis occurs in the majority of cases. The leukocytes also will usually be considerably increased. According to Howard[15] adventitious sounds in the lungs are comparatively rare. They were heard in only seven of the 56 cases studied by him.

The diagnosis of injury to the thoracic duct is made on the finding of chyle in the fluid withdrawn by aspiration from the pleural cavity. Fortunately, it is a rare complication. Sherman[16] has analyzed 11 cases of chylothorax in children including one case of his own.

Treatment.—Heuer[17] has written an excellent article on penetrating wounds of the chest and the reader is advised to consult his article for details of the treatment of such conditions. The war has to a certain extent revolutionized and standardized the treatment of these conditions. Because of their relative infrequency in childhood only general principles rather than details of treatment will be discussed here. It is now rather generally agreed that all open sucking wounds should be closed as rapidly as possible in order to convert an open pneumothorax into a closed one. This should be done

in conjunction with a preliminary débridement of the wound. Closed wounds produced by small projectiles can be treated expectantly unless there is positive evidence (1) that the missile, a fragment of bone, or other foreign material is retained in the lung, or pleural cavity; (2) that alarming hemorrhage is occurring, or (3) that, if in a late case, infection has already occurred necessitating operation. Small missiles, such as rifle or revolver bullets, are usually relatively innocuous even when retained in the lung; and operation for their removal should be undertaken only if they are readily accessible. Roux-Berger,[18] however, considers that all penetrating wounds of the chest should be operated on save in the most exceptional circumstances; the exception comprises bullet wounds with punctiform orifice, presenting no sign of hemorrhage and when the location precludes the possibility of the necessity of a reparative operation (for instance, on internal mammary vessels, or diaphragm). He considers also that every intrapleural missile should be removed but that it is not so necessary to remove a small bullet imbedded in the lung.

When hemorrhage has been extensive severe shock is present which must be vigorously combatted in accordance with the same general principles of the treatment of shock when arising from any condition. Hemothorax is probably best treated by aspiration especially in a case in which there is a closed wound presenting no positive indication for thoracotomy. The extravasated blood provides an ideal culture medium for bacteria and must often be an important factor in the production of an empyema. Bastianelli[19] believes that after aspiration of the blood air should be injected to take its place. He thinks that the compression exerted on the lung in this way prevents hemorrhage. Air should not be injected indiscriminately, but preferably under conditions which permit an exact knowledge of the intrapleural pressures obtained. Otherwise a disaster may occur from the injection of too much air. A pneumothorax apparatus of the general type of that devised by Singer will be satisfactory. At all events, whether simple aspiration or the Bastianelli method is used, it is very important to keep a close watch on the patient to detect any recurrence of hemorrhage. If signs of fluid promptly return and the aspirating syringe shows fresh blood to be present, serious intrapleural hemorrhage is probably occurring. In such a case operative intervention is the safest procedure.

The incision is best made in the neighborhood of the wound, which should be excised. If the ribs have been splintered the loose fragments should be removed. If not, access to the pleural cavity may be accomplished by either a subperiosteal rib resection or a thoracotomy with spreading of the ribs by means of a "rib spreader" (Lilienthal's major thoracotomy). Careful search should be made for the source of the hemorrhage, recalling that it may come not only from the lung but also from the internal mammary artery, an intercostal, any of the great vessels, the heart, or the liver. Wounds of the lung which are bodies imbedded in the lung can be removed at the same time. It

is especially important to remove fragments of bone or particles of clothing that may have been carried into the lung, since this type of foreign body is very likely to be followed by abscess formation. Bleeding from other sources than the lung is handled by ligature or suture as the particular case may require. In closure of the wound it is imperative that the pleura be tightly closed. Layer closure of the structures of the thoracic wall is the ideal. If the pleura is not made air-tight infection is bound to occur. Heuer[17] states that of his own series of 160 cases of penetrating war wounds of the chest which were sewn up tightly without drainage, infection did not occur in a single case. Dobson,[20] however, says that Gask and Wilkinson had 22 post-operative empyemas in 67 thoracotomies with immediate closure (32 per cent.); Anderson had 12 in 58 primary closures of the thoracotomies (29 per cent.); and Duval had 9 cases in 29 thoracotomies with complete closure (31 per cent.).

One of the most striking contributions furnished by the war to surgery was that which concerned the operative treatment of penetrating injuries of the thorax. Whereas previous to the war the treatment of these conditions was very largely conservative and expectant, the operative indications have now been very greatly extended. Duval[21] has been one of the most radical and persistent advocates of bold operative attack for the removal of retained missiles from the lung even in late cases. Others, however, including Tuffier, Piery, Petit de la Villéon,[22] etc., on the basis of large experiences during the war, are much more conservative and advocate the late removal of missiles only when definite symptoms can be ascribed to them. Elliott[23] found that in the absence of infected hemothorax men with missiles retained in the lung are returned to duty as quickly as those without. The most favorable time certainly for the removal of the foreign bodies is in the preinfective stage rather than after infection has become well established.

The treatment of infected hemothorax is in principle essentially the treatment of empyema, which will be discussed later. It may be stated here, however, that considerable discussion has arisen concerning the most suitable time to institute drainage. Grégoire and Courcoux[24] state emphatically that "a pleura ought not to be drained until the day when it suppurates frankly," while others contend that drainage should be instituted as soon as the presence of infection can be demonstrated. In our own opinion drainage should be by a closed method if instituted early before a stage of frank suppuration and before adhesions have formed.

Prognosis.—Heuer in his summary of the war literature states that the mortality in large open wounds of the chest with adequate treatment is about 25 per cent.; in small open and closed wounds it is less than 10 per cent.

Injuries to the thoracic duct are relatively uncommon and usually recover spontaneously. Most of the reported injuries have occurred in the neck and simple packing has generally been followed by healing.

Ligation has been practiced in some, and Keen has successfully sutured an operative tear. The majority of those which occur in the thorax are in association with very severe injuries, such as fracture of the spine; and ordinarily do not call for special treatment.

The treatment of combined thoracic and abdominal wounds will vary considerably, depending upon the clinical picture in the particular case. Probably in all cases the abdominal cavity should be explored, unless the case is seen for the first time several days after the accident and no untoward symptoms have developed. The expectant treatment for such injuries was discarded during the war because of its bad results. The abdominal viscera which are most likely to be injured are those which occupy the upper part of the abdominal cavity. These are usually accessible through a transthoracic incision, especially if made on the left side, which also allows the easiest repair of the diaphragm. In left-sided combined injuries, therefore, a thoracic incision is to be preferred, followed later by an abdominal incision if necessary to complete the repair of abdominal viscera. On the right side, however, because the liver will interfere with a satisfactory exploration of the abdomen through a transthoracic incision, in general it will be better to explore the abdomen through a separate laparotomy incision.

Wounds of the heart should be operated on as soon as diagnosed. G. T. Vaughn[25] in 1909 found reported 150 cases, including his own, of suture of wounds of the heart with 35 per cent. of recoveries. The various incisions which have been used for an approach to the heart will be found discussed in most text books on operative surgery. The article by Matas[26] in Keen's Surgery discusses at some length the various incisions which have been proposed.

As for other measures necessary in the treatment of penetrating wounds of the chest emphasis should be placed particularly on the use of tetanus antitoxin. The manner in which most of these wounds are received, namely, by projectiles of various kinds and in street accidents, makes it imperative that the patient be protected against the development of tetanus in so far as it may be possible. Rest in bed should be insisted on. A semi-recumbent position will often be more comfortable than a flat one. Morphine may be given to control excessive coughing, and sometimes strapping of the chest with adhesive will do much to control pain which usually is not severe.

Fractures and Dislocations of the Ribs and Sternum have been discussed elsewhere in the general chapter dealing with fractures.

DISEASES OF CHEST WALL

Simple Inflammations.—Simple inflammations involving the skin and subcutaneous tissues of the thorax differ in no essential respects from those elsewhere on the body surface and therefore will not be discussed particularly in this section. Mention should be made, however, of the fact that there is a special tendency for carbuncles to develop on the back between the shoulder-blades, but these are comparatively rare in children.

Acute inflammations of the chest wall itself are usually considered serious and to be associated with a grave prognosis. Thus, Riedinger and Kümmell,[27] for example, state that of 10 cases treated at the Eppendorf Hospital during a period of six years only two recovered. The author's experience, however, has been very different. One often finds a spreading inflammation of the chest wall as a sequel of empyema, not only as the classical "empyema necessitatis" but also in certain cases following drainage. The infection may travel considerable distances between the ribs and the large muscles, the pectorals, latissimus dorsi, etc. In my experience such cases show a marked tendency to abscess formation and respond quickly to incision and drainage. I have seen also two cases of subpectoral abscess, due probably to improperly given salt solution, both of which healed promptly after incision and drainage. Almost always an abscess of the chest wall tends to perforate externally and not into the pleural cavity. In general the most serious phlegmonous inflammations of the chest wall are those which arise from suppurating axillary lymph glands. The diagnosis in the early stages may be difficult because of the deep-seated location of the abscess. Usually some degree of swelling will appear in the painful region within a few days after the onset of the pain, and a carefully used aspirating syringe will withdraw pus. The possibility of an "empyema necessitatis" must always be borne in mind. The principles of treatment are the same as those involved in treating suppurating processes elsewhere. Care must be exercised of course not to infect the pleural cavity by accidental puncture.

Osteomyelitis of Ribs and Sternum

Idiopathic pyogenic infections of the ribs and sternum are much less common than are the granulomatous infections. They occur perhaps most often as sequelæ of typhoid fever. In Keen's[28] 237 collected cases of typhoid bone infections the most commonly involved bones in their order of frequency were found to be: Tibia, ribs, femur, ulna and humerus. It is noteworthy, however, that not a single case of infection of the ribs occurred before the age of 20. It is still more rare for spontaneous infections of the ribs to occur with organisms other than the typhoid bacillus. A primary staphylococcus osteomyelitis of the twelfth rib in a girl, seven years old, was recently seen in the St. Louis Children's Hospital. A definite sequestrum was found. After its removal the child made a complete recovery. The accompanying photographs illustrate the condition. The author has seen one case in which a staphylococcus infection of a rib followed a blow from a baseball. There was no evidence of an associated fracture of the rib. In almost every case of empyema in which drainage has been instituted some degree of infection of the rib occurs. This is especially marked in those cases in which the marrow of the rib has been exposed to infection by rib resection. In such cases it is very common to find that sequestra are responsible for the continuance of a long-standing sinus. Typhoid infections as a rule are accompanied

by less fever than the other pyogenic infections and pain may be relatively insignificant. The leucocytes also may not be much increased.

In the diagnosis of pyogenic infections of the ribs the most important conditions to differentiate are empyema and tuberculosis of a rib. Sarcomas of ribs also sometimes simulate acute infections. The diagnosis of these various conditions will be found discussed under their respective headings. The *x*-ray occasionally is of value but generally it will not aid much in the diagnosis.

FIG. 16.—Pointing abscess from spontaneous staphylococcus osteomyelitis of the twelfth rib. (From St. Louis Children's Hospital.)

Suppurative infections of the ribs and sternum should be treated radically according to the same principles employed in osteomyelitis elsewhere. In general, and particularly in the typhoid cases, it will usually be found more satisfactory to resect an entire segment of rib rather than to attempt to eradicate the local lesion itself. When more conservative methods are applied to inflammatory conditions of the ribs the usual result is failure. Care of course should be exercised in order not to tear the pleura and infect the pleural cavity.

TUBERCULOSIS OF RIBS AND STERNUM

Tuberculosis is the most common inflammatory condition involving the ribs and sternum. According to Billroth and Menzel[29] there were 184 cases of tuberculosis of the sternum, ribs or clavicle out of a total of 2106 cases of tuberculosis of bone. Out of 1795 cases of bone

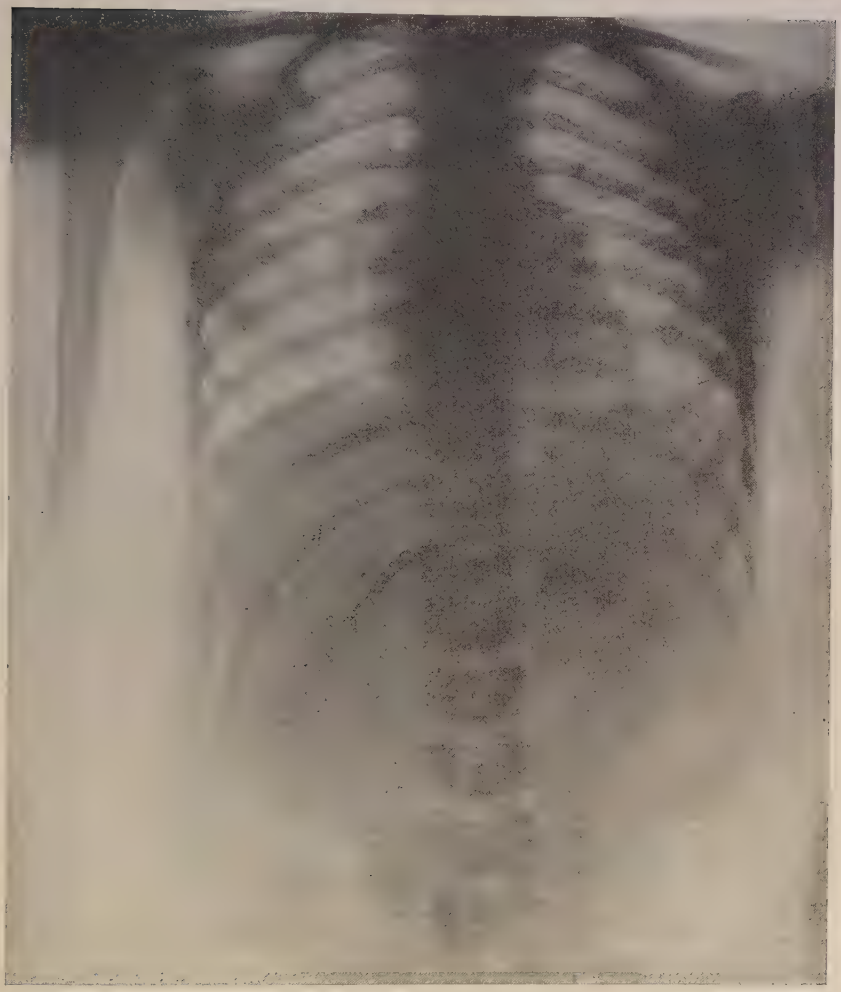


FIG. 17.—Skiagraph of chest of patient shown in Fig. 16. Involved rib slightly retouched.

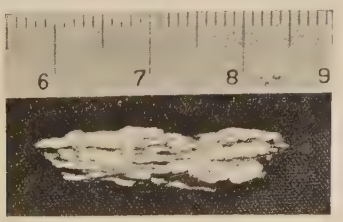


FIG. 18.—Photograph of sequestrum removed from patient in case shown in Fig. 16. Centimeter scale.

tuberculosis at the Eppendorf Hospital 104 involved the sternum and ribs. It occurs most commonly in middle life but it is not infrequently seen in young adults and in children. It occurs both as a primary condition and secondary to tuberculosis of the pleura. It begins usually as a small central focus which extends slowly to the periphery. The neighboring periosteum is usually greatly thickened as is also the fascia. Sequestra as a rule are not formed. The tuberculous abscesses may travel considerable distances to open spontaneously. In a case of a young man in my care, an abscess evidently arising in a costal cartilage travelled down beneath the right rectus abdominis muscle

Fig. 19.—Osteomyelitic rib-abscess. (After Carl Beck in "Surgical Diseases of the Chest.")

and gave an impression of an intra-abdominal tumor. Almost invariably these abscesses open and discharge their contents externally rather than into the pleural cavity. More than one rib may be involved at the same time. Tuberculosis of the sternoclavicular joint with a considerable involvement of both sternum and clavicle is not uncommon.

The subjective symptoms are usually not marked. The first and only thing noticed by the patient may be a painless, oblong, soft swelling which fluctuates but is not red. If the swelling is opened, characteristic curdy pus will be evacuated and roughened necrotic bone may be felt or seen at the bottom of the abscess. Evidences of tuberculosis elsewhere in the body may also be found. As a rule the greatest difficulty in diagnosis is presented by the cases with long

sinuses. Injection of these sinuses with bismuth paste and examination with the *x*-ray, particularly if stereoscopic plates are made, will often show that the sinus leads to a rib.

The prognosis varies considerably in different cases. As far as life is concerned it is a question almost entirely of the extent of tuberculous involvement elsewhere. If the process is confined to a single rib the prospect of complete healing is good if the case is treated radically.

Treatment.—This consists in a radical resection of the portion of rib involved. Less radical measures such as curetment, etc., are to be condemned because they do not accomplish healing. Moschcowitz[30] has recentlyshown in a convincing manner the necessity of removing the entire costal cartilage in cases in which that is involved. Operations of excising only a portion of the cartilage are of little or no avail. He advises, furthermore, that if any portion of the sixth, seventh, eighth, ninth or tenth costal cartilages is involved all of these cartilages should be removed in order to promote prompt healing. In the case of the sternum more conservative measures may be tried if the involvement is slight; but if at all extensive, a considerable portion of sternum around the diseased portion should be excised. The author several times has resorted to rather extensive excisions of portions of the sternum and has never seen any bad effects. In cases in which the clavicle is involved a considerable amount of the bone can be removed even without any resultant disability. In one case I removed the inner third of the clavicle and a considerable portion of the manubrium without any evident impairment of function. The local surgical treatment should of course be combined with general hygienic treatment.

Syphilis of the Sternum and Ribs

Syphilitic lesions of the sternum and ribs occur less frequently in children than in adults. The condition may simulate tuberculosis so closely that it is impossible on clinical grounds to make a differentiation. A large, soft, fluctuating mass may be present over the sternum or along a rib. The Wassermann reaction will of course help to establish the diagnosis which will be confirmed by the prompt subsidence of the tumor on anti-syphilitic treatment. In a recent case of syphilis of the sternum in a colored man under my observation a considerable amount of pain and tenderness at the site of the tumor was complained of. Pain, however, is usually not marked.

Actinomycosis

Actinomycosis is especially rare in children and the condition does not merit more than brief comment here. It resembles tuberculosis closely and when it involves the ribs the process is usually secondary to a pulmonary infection. A positive diagnosis is made by finding the characteristic sulphur granules in the pus which microscopically reveal the ray fungus. The organism may also be cultivated from the sulphur granules. I have seen only one case of actinomycotic involvement of the ribs. In that case multiple ribs were affected.

TUMORS OF THE CHEST WALL

Benign Tumors

The tumors of the chest wall, for clinical reasons, are usually classified into those which arise from the soft parts and those which originate from the bony wall. Practically all of the various types of benign tumors have been found to arise in the chest wall. The most common ones in children are angioma (both hemangioma and lymphangioma), dermoid, lipoma, and fibroma. Keloid, neuroma, and particularly the neurofibroma of Recklinghausen are conditions affecting adults rather than children.

Angiomata.—Nevi occur in the skin of the chest just as elsewhere in the body, and they require no special comment. Of special interest, however, are the large hairy pigmented moles, the so-called "nevi pilosi." They may sometimes be of considerable size with hair several inches long. A common location is the back and shoulders. Removal of these pigmented moles is usually indicated not only for cosmetic reasons but also because they all should be regarded as potentially malignant. Surgical excision is the best and safest method of dealing with all pigmented moles. For the ordinary nevi radiotherapy is usually successful.

Cavernous Hemangioma.—This occurs on the chest next in frequency to the head. These tumors are usually flat and slightly elevated above the skin, and they may be either light or dark red in color. They are commonly not more than 1 or 2 cm. in diameter, but sometimes they become very large. Growth often begins suddenly and the tumor increases very rapidly after a long period of inactivity. Females are more commonly affected than males. Hemangiomata arise either in the skin itself or in the subcutaneous tissue. In the latter instance the color may not be evident until, after progress of the tumor, the skin itself is affected and the characteristic bluish shimmer appears. Hemangiomata sometimes ulcerate and give rise to very severe hemorrhage which in some cases has been fatal. Because of their tendency to progress, in addition to the danger of hemorrhage, an attempt at removal should always be made. The small ones are usually easily excisable. Practically all of them, however, both small and large, respond readily to radiotherapy with either the *x*-ray or radium. This is the method of choice in the large ones because of its simplicity and relative safety in the hands of experts. Various other methods have been suggested, actual cautery, application of caustics, injection of boiling water, carbon dioxid snow, etc.

Lymphangiomata.—These tumors when found in the chest wall seem to arise usually from the lymphatics of the axilla. They may even be connected with the mediastinum. They are very similar in structure to hemangiomata except that their contents are lymph instead of blood. They almost always extend beneath the pectoral muscles. They may progress to form large cystic tumors. The treatment is essentially the same as that already outlined for the hemangiomata.

Dermoid Cysts.—When these occur on the thorax they are usually extensions from the anterior or posterior mediastinum. They will be discussed more completely in connection with the surgery of the mediastinum.

Lipomata.—These tumors on the chest, and especially on the back, are common in adults but comparatively uncommon in children,

Fibromata.—These also are relatively uncommon in children. The diagnosis of both lipoma and fibroma is usually easy in this region. and the most satisfactory treatment is excision.

Osteoma.—True osteomata of the chest wall are very rare. The supposed bony tumors nearly always contain some cartilage.

Chondroma.—Chondroma is the more common benign tumor which arises from the bony chest wall. Although some of these tumors are benign, others show a tendency to recur after excision and still others give rise to metastasis. These cartilaginous tumors, therefore, afford a sort of link between benign and malignant processes. Of the cartilaginous tumors the malignant ones are more common than the benign. The most frequent sites of origin of these cartilaginous tumors of the chest wall are the cartilaginous portions of the ribs at about their junction with the sternum, and the scapula. Deganello[31] has collected 39 cases of chondrosarcoma of the scapula, including one of his own. Three of this series were children. The variations presented by the different cases, both clinical and pathologic, are well described. Benign chondromata grow slowly and may become enormous. The symptoms produced are chiefly those of pressure against adjacent structures. The tumors are usually hard, rounded and lobulated. Some, however, become softened by mucoid degeneration. The diagnosis of a cartilaginous tumor is usually easy because of the characteristic location, shape and consistency. It is often extremely difficult, however, if not impossible, to differentiate between a benign and a malignant one; and even to obtain an adequate conception of the extent of the tumor from superficial examination is impossible. The most rational and satisfactory treatment of these tumors is by excision. The operation usually, however, becomes much more extensive than the surgeon inexperienced in this type of cases had supposed it would be. It frequently carries with it also the necessity of widely opening the pleural cavity. For these reasons it should never be undertaken lightly; and except at the hands of those who are experienced in thoracic surgery the mortality will be surprisingly high. Hedblom[32] has an excellent article on the subject of tumors arising from the bony chest wall to which reference should be made for the details in the operative treatment of these tumors.

Malignant Tumors

Sarcoma.—Hedblom[32] has analyzed a series of 213 cases of tumor of the bony chest wall, of which 48 were from the Mayo Clinic. Of the total number 131 were diagnosed as sarcoma and 40 as chondroma; in other words, sarcoma and chondroma represent a little

more than 80 per cent. of all reported tumors of the bony chest wall. The tumors originated in the ribs about four times as frequently as in the sternum. Of the reported cases in which the age was given, 28 occurred before the age of 20. Hedblom states that 8 per cent. of the sarcomata of the Mayo Clinic series were combinations of chondroma and sarcoma and probably originated as chondroma. The pathology of these sarcomata does not differ essentially from that of sarcomata arising in other bones.

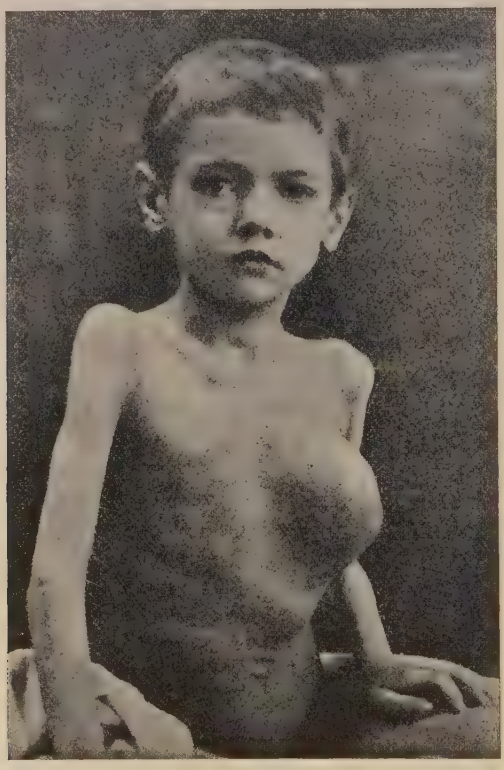


FIG. 20.—Sarcoma of the chest wall. (After Carl Beck, "Surgical Diseases of the Chest.")

Aside from the presence of a tumor Hedblom states that pain is the most characteristic symptom; it was present in 50 per cent. of his own cases. Dyspnea and effusion are only rarely present. Severe pain may be present before any appearance of a tumor, and a mistaken diagnosis of intercostal neuralgia has often been made. In some cases it is difficult to distinguish between a thoracic aneurism and a pulsating sarcoma. The *x*-ray is of great value in making a diagnosis. The final diagnosis of course will depend largely upon the microscopic examination of the tumor.

Treatment.—Radical excision of the tumor seems at present to be the best procedure, although, as is the case in other bone sarcomata,

the results obtained by excision are not particularly gratifying. Recurrence is the rule, but yet a few patients have had no return of the growth after a period of several years. Hedblom[32] reports one case still free from recurrence eight and one-half years after operation and states that another patient, aged 38, presented himself with a sarcoma of the anterior chest wall and a history of having had a sarcoma removed from that location at the age of six years with three later operations for recurrence. Hedblom has not noted any strikingly beneficial effects of radiotherapy. We have recently, however, seen a sarcoma (?) of the chest wall as large as a child's head disappear completely under radium treatment. This patient had had an operation performed elsewhere a few weeks previously, but because of the extensive involvement an excision was not undertaken. The report sent to us was that a piece of tissue removed showed the tumor to be a small round-celled sarcoma. The patient would not consent to any further operative procedure.

Carcinoma of the chest wall, because of its extreme rarity in childhood, will not be discussed here. Chrétien[33] has described a congenital mucoid cyst of the presternal region; and Masse[34] has reported what he calls a congenital diffuse lipoma of the thoracic wall. Echinococcus cysts of the chest wall have been reported but the condition is so rare in this country that no comment here is necessary.

DISEASES OF PLEURA

Empyema, or Suppurative Pleurisy

Inflammations of the pleura are exceedingly common in children as well as in adults, and suppurative pleurisy (empyema) is one of the most common affections in childhood requiring surgical treatment.

Etiology.—Like purulent inflammations of the peritoneum, empyema is usually secondary to an infectious process which has extended from some adjacent focus either by a spread through lymphatics or by the rupture and discharge of purulent material from an abscess in the immediate neighborhood of the pleuræ. In the majority of cases it accompanies or follows pneumonia. In rare instances it is considered to be primary. But the conception of primary empyema is essentially a clinical one which is seldom, if ever, supported by careful necropsy examinations. Even the clinical conception in most instances is incorrect, since there has usually existed an antecedent infection, often in the throat. The difficulty in recognizing by clinical methods small areas of pneumonia or small septic pulmonary infarcts places the conception of a primary empyema on a still more slender basis.

It may occur at any age. It has been found in infants within a few days after birth. Gee[35] analyzed 169 cases of pleurisy with effusion in children under 10 years of age at St. Bartholomew's Hospital and found 85 purulent and 84 non-purulent. But of 78 cases under 5, 53 (68 per cent.) were purulent; and of Carpenter's series of 116 cases under 5, 77 (66 per cent.) were purulent. Cruveilhier[36] reported finding false membranes on the pleura of a dead fetus whose mother had suffered

from a febrile attack. F. Weber[37] in the middle of the last century called attention to the frequency of pleural inflammation in infancy. The preponderance of incidence in males, which is so striking in adults, is not observed in childhood. Wilensky[38] in an analysis of 299 cases of empyema occurring in the Mt. Sinai Hospital, New York, found the incidence according to age to be as follows:

Years	Cases	Deaths
Under 1	44	21
1 to 2	67	21
2 to 3	29	12
3 to 4	18	
4 to 5	13	2
5 to 10	29	1
10 to 20	26	4
20 to 30	34	7
30 to 40	16	5
40 to 50	11	4
50 to 60	9	5
60 to 70	3	

Youngest 5 weeks, oldest 64 years.

The various kinds of bacteria found in empyemic effusions differ considerably, although a striking uniformity may occur during a pandemic such as the recent influenza. At that time, for example, hemolytic streptococci were found in almost all cases. As a rule, however, in ordinary times the pneumococcus vies with the streptococcus in frequency. Netter[39] found in a study of 110 cases the following incidence:

	Cases
Streptococcus	51
Pneumococcus	32
"Saprogenic" bacteria	15
Tubercle bacillus	12
	110

The percentage of incidence of different organisms in children and adults was as follows:

Bacteria	Per cent.	
	Children	Adults
Streptococcus	17.8	53.0
Streptococcus and pneumococcus	3.6	2.5
Pneumococcus	53.6	17.3
Staphylococcus	....	1.1
Tubercle bacilli and others	14.3	
Putrefactive organisms	10.7	8.0
Tubercle bacilli and putrefactive organisms	....	25.0

From these results it would seem that in children the most common organism is the pneumococcus but in adults the streptococcus. It must be borne in mind, however, that at the time these analyses were made (1889) bacteriologic differentiation between the pneumococcus and streptococcus was not very certain. An analysis based on modern technique would be instructive. Wilensky[38] records the bacteriologic findings in 574 cases of pleural effusion of all ages at Mt. Sinai Hospital as follows:

	Cases
Pneumococcus	289
Streptococcus	123
Streptococcus mucosus capsulatus	10
Staphylococcus aureus	52
Staphylococcus albus	29
Staphylococcus citreus	5
Bacterium coli	4
Bacillus typhosus	2
Bacillus proteus vulgaris	2
Bacillus mucosus capsulatus	2
Bacillus influenzæ	2
Bacillus tuberculosis	7
Bacillus fusiformis (of Vincent)	2
Bacillus fluorescens liquefaciens	5

Most of the remainder were unidentified organisms.

Holt[41] presents the following interesting tabulation concerning empyema in 154 cases of empyema in children under three years of age at the Babies' Hospital, New York, which agrees with Netter's[39] results in showing that the pneumococcus is the most frequent organism in the empyema of children:

	Cases	Deaths	Mortality, per cent.
Pneumococcus	77	43	56
Streptococcus	24	19	79
Staphylococcus	12	6	50
Influenza bacillus	1	0	0
Tubercle bacillus	1	0	0
Mixed infections:			
Pneumococcus and staphylococcus	7	6	62
Pneumococcus and streptococcus	5	2	
Pneumococcus, staphylococcus and streptococcus	2	2	
Streptococcus and staphylococcus	6	2	
Streptococcus and proteus	1	1	
No record	18	6	

Pathogenesis.—A. V. Moschcowitz,[40] having noted that abscesses, usually minute, are frequently found at necropsy immediately beneath the visceral pleura, has suggested that empyema is due to a rupture of such an abscess into the pleural cavity. Possibly such an explanation may hold for certain cases, but it would seem that in the majority of cases such an assumption would be unnecessary. Often within a day or two following the pneumonia there is an exudate in the pleural cavity containing myriads of streptococci, a period too soon apparently for the abscesses to have formed and ruptured. Furthermore, it is well known that streptococci are widely disseminated throughout the lymphatics of the pleura in early cases of streptococcal pneumonia[42] and it would seem easy for them to pass through the pleura and induce an exudate in the pleural cavity without the preliminary necessity of forming an abscess.

In this connection some experiments which I have recently carried out[43] are of interest. A model thorax was constructed by the use of a pair of dog's lungs and a bell-jar which allowed a direct study of at least some of the principles involved in the formation of pleural exudates. A pair of lungs was removed from a dog immediately after death, and the trachea was tied over a glass tube that passed through a rubber stopper at the top of the bell-jar. A rubber tube was connected with a glass tube that passed through a rubber stopper in an opening near the bottom of the bell-jar. This rubber tube was connected with an ordinary filter pump by which air could be exhausted from the bell-jar. With the lowering of the pressure in the bell-jar, air rushed down the trachea and inflated the lungs. By means of a T-tube interposed in the connection with the filter pump, connections were also made with a water manometer and with another open tube, which, by alternate clamping and releasing, permitted the alternate inflation and deflation of the lungs at any desired "intrapleural" pressure. By this means they could be made to undergo regular rhythmic respiratory movements. When edematous lungs were used in the model, a copious "pleural exudate" could be produced within the bell-jar which was always most marked during and immediately after the expiratory act. When a solution of methylene blue was poured into the trachea it made its appearance in the pleural exudate very quickly. Usually a single inspiration would result in the appearance of the dye in the visceral pleura; and if the lungs were held in a condition of moderate inflation, the staining of the pleura would be seen to spread very rapidly over rather wide areas from single small foci. As soon, however, as expiration was induced by allowing air to enter the bell-jar, blue-stained exudate was seen to pour from the lungs.

The rapid appearance of the dye on the visceral pleura during inspiration seemed to be explainable perhaps on the basis of a filling of the pleural lymphatics as a result of an aspiration effect induced by the diminished pressure outside the pleura. The explanation of the greater formation of exudate during the process of expiration is more

difficult. It is clear that if the pleura becomes saturated with fluid during the process of inspiration, then the sudden reduction in surface necessitated by expiration cannot be accomplished unless this fluid is squeezed out. The exudate, therefore, which under the conditions of the experiment pours out copiously during expiration, represents fluid that has been squeezed out of the edematous pleura as a result of the sudden diminution in surface necessitated by the act of exhalation.

It is recognized that the conditions of the experiment are not identical with those which are encountered in life, since in the model the cohesive force is absent which is an important factor in keeping the visceral and parietal pleuræ in contact during life, and also the lungs in the experiment are, of course, dead. The latter fact apparently introduces many complicating factors, such as increased diffusibility of the exudate through the lung and pleura. Nevertheless, lungs which are attacked by severe infections, such as in the streptococcal bronchopneumonias, frequently contain considerable areas of necrosis even during the life of the patient. The phenomena which have been noted in the experiments, therefore, must often occur to a more or less degree during life.

Moreover, it is in those acute pulmonary inflammatory conditions in which the dyspnea is most marked that the most rapid accumulation of pleural exudate occurs, as, for example: In the streptococcal bronchopneumonias. This fact seems to conform well with the idea here being developed, namely, that the presence of a minus pressure in the pleural cavity would tend by aspiration to draw fluid from a pleural surface which was edematous. Since the intrapleural pressure diminishes still more as the inspiration becomes deeper, one might expect more fluid to be aspirated into the pleural cavity in a condition of dyspnea associated with an increased depth of inspiration than under normal conditions. If, in addition to the dyspnea, the added factor of impaired inflation of the lungs were present so that during inspiration they could not be expanded to meet completely the depressed diaphragm or the thoracic walls in their changed position, the aspiration of fluid into the pleural cavities might follow to a still greater degree. It is interesting that in the bronchopneumonia due to hemolytic streptococci the factors are present which would make for a rapid accumulation of pleural exudate. It has been a common observation in this condition, at least in the case of adults, that, in spite of most extreme inspiratory efforts, the vital capacity remains low, a fact which demonstrates the impaired ability to inflate the lungs. The pathologic studies of MacCallum[42] and others have shown the existence of a marked peribronchiolitis with numerous areas of atalectasis, a finding which would seem to indicate that the occlusion of air passages by both surrounding and contained exudate would be sufficient in many cases to prevent normal inflation of the lungs.

The idea expressed here of the influence of the respiratory movements on the formation of pleural exudates is very different from the idea of the "lymphatic pump," as expressed by West;[44] for in the

latter idea the respiratory movements are thought of as "pumping" fluid out of the chest by sending it along the lymphatics which absorb it. The accumulation of fluid, according to West,[44] would occur then in one of two ways: "Either it may be poured out into the pleura in larger quantities than the pump can remove, that is, its amount may be abnormal, or the amount of fluid not being above the normal, the pump may be defective."

The easy passage of fluids and dyes from the lung into the pleural cavity, as demonstrated in these experiments, in addition to the well-known presence of organisms in the visceral pleura in cases of pneumonia, makes the assumption of antecedent subpleural abscesses unnecessary in explaining the pathogenesis of empyema, although in some cases the rupture of these abscesses may be the chief factor. Again, in experiments performed in 1918,[45] while producing empyema in dogs by the direct inoculation into one pleural cavity of pleural exudate containing streptococci, evidence was repeatedly obtained of the passage of organisms from one pleural cavity into the pericardial cavity and from there into the other pleural cavity without the presence of any demonstrable subpleural abscesses.

Pathology.—The essential feature of empyema is the presence of pus in the pleural cavity. It constitutes therefore an abscess of the pleural cavity. Marked variation in the amount of the exudate is encountered, from a few cubic centimeters to several liters. The amount is governed to a great extent by the volume of the pleural cavity; so that, as might be expected, smaller effusions in general are found in children than in adults. To some extent also the chronicity of the infection determines the amount of the fluid, although too much reliance cannot be placed on this. In general, however, the largest effusions occur early in the course of the disease, and they are likely to be relatively thin. They may be serofibrinous, blood-tinged or distinctly hemorrhagic. Such fluids are noted especially in the early stages of an empyema due to hemolytic streptococci, and even at a very early stage they may show very large numbers of these organisms. The thin fluids tend to separate into layers rather quickly after removal and a thin sediment of pus will collect at the bottom with a supernatant layer of serohemorrhagic fluid. The leukocytes in such pus will be found for the most part to be necrotic and only slight phagocytosis occurs. Red blood corpuscles are often present in considerable numbers.

MacCallum[42] has described the character of the fluid exudate in the streptococcal cases as follows: "Numerous epithets have been applied to it—it is like thin pea soup, like turbid urine, like unstained bouillon, like muddy water, but generally like thin pea soup. It has often a greenish cast and the granular sediment which can be stirred up in a cloud tends to settle in the bottom of the pleura. Strands or flakes of fibrin float up in this or hang from the wall. Later it rapidly becomes more turbid and thick and assumes a more purulent character, and especially when it is confined in localized areas by adhesions it is

often thick whitish-green pus. When the pleural cavity has been laid open by resection of the rib the fluid changes somewhat, and if it is secondarily infected with putrefactive organisms it becomes very foul and often blackish green." Deposition of fibrin occurs on both the visceral and parietal pleuræ and enormous thickening may occur so that the pleura may at times be 2 or 3 cm. thick. Fibrinous adhesions are almost always present, and, especially in the streptococcal cases, multiple pockets of pus are often found. Also, as emphasized by MacCallum,[42] in the streptococcal cases there is a very striking tendency for the exudate to become organized early. This is in rather marked contrast to the pneumococcal cases. The character of the fluid exudate in the pneumococcal cases is also strikingly different from those due to the streptococcus, at least in so far as the clinician is concerned. Almost never does he see serofibrinous pleural exudates of pneumococcal origin. This is doubtless in part due to the fact that pneumococcal empyema is not generally recognized until late in the course of a pneumonia, while, on the contrary, the streptococcal exudates very early may be so massive that they are easily recognized, and they may even conceal the existence of a pneumonia.

The marked frequency of pocket formation in the streptococcal cases was noted in all the United States Army camps during the severe epidemic of streptococcal infections of the respiratory tract in the winter of 1917–1918. In reply to the questionnaire on empyema sent out by the Surgeon General,[46] Camp Sevier reported that in all of the first 50 necropsies in cases of empyema, substernal pockets of pus were found. These so-called substernal pockets of pus were also especially noted at Camps Funston and Custer.

Various types of lung involvement may be found associated with the empyema, depending to a considerable extent on the nature of the infecting organism. In the pneumococcal cases, at the time of recognition of the empyema, the pneumonia is usually in a stage of resolution or gray hepatization. In the streptococcal cases, however, an exceedingly varied pathology may be found. The pathology of the pneumonia will not be discussed in great detail here, since it is given fully in another part of the System. The essential feature of the streptococcal pneumonia apparently is that it is not lobar, in the sense of the ordinary pneumococcal lobar pneumonia, but it is in reality a "peribronchiolitis" with patches of pneumonia which may coalesce at times to suggest a lobar distribution. The walls of the bronchioles are infiltrated with leukocytes, and their lumina are plugged with masses of necrotic material, leukocytes, etc. Atelectasis is common, usually patchy, but it may be so extreme as to involve an entire lobe or even an entire lung. Abscesses of the lung, usually multiple, are common in the streptococcal cases and should not be confused with the interlobar pockets of pus which are also common. Common complications which may be present have been shown by Stone[47] in an analysis of 100 necropsies at Fort Riley which occurred during the epidemic of streptococcal infections:

	Per Cent.
Nephritis, parenchymatous acute diffuse or exacerbation of chronic	47
Pericarditis, serofibrinous or purulent	46
Pneumonia active in both lungs	45
Empyema, bilateral	19
Abscess of lung	15
Peritonitis, metastatic diffuse purulent	13
Substernal pus pockets	11
Endocarditis, ulcerative or vegetative acute	3
Tuberculosis, pulmonary active	3
Meningitis, subacute basilar	3

Less common complications are brain abscess, parotitis and subphrenic abscess. Spontaneous perforation of an empyema through

Fig. 21.—Empyema necessitatis, following pleuropneumonia in a child of 3, finally cured by extensive resection. (After Carl Beck, "Surgical Diseases of the Chest.")

the chest wall (empyema necessitatis) was formerly a common sequel to empyema but now it is observed only rarely (Fig. 20). Diaphragmatic hernia has been reported occasionally as a complication. It is natural in these cases to assume that probably the diaphragm has been torn during the operation for drainage, but yet MacNab's[48] interesting case seems to preclude that possibility, because of the height at which the incision was made. The patient was a girl 15 years of age. The incision for drainage was made in the third intercostal space anteriorly about 2½ in. below the clavicle. She made a good recovery from the empyema. Nearly three years later she was suddenly seized with vomiting after a hearty meal. Death occurred in twenty-four hours. Necropsy showed the entire stomach in the chest, practically filling left pleural cavity. There was an opening in the left tendinous portion of the diaphragm. The hernia had probably been present for a year before death, because of the patient's com-

FIG. 22.—Skiagraph of diaphragmatic hernia apparently as a sequel to a drainage of an empyema. Erect posture. (From St. Louis Children's Hospital.)

FIG. 23.—Skiagraph of patient shown in Fig. 21, recumbent, showing fluid level.

plaint of pain in the chest after each meal and gurgling sounds under the clavicle. A case under observation recently at the Saint Louis Children's Hospital on the service of Doctor Clopton was that of a child who entered the hospital with a discharging sinus of the left thorax at about the level of the sixth interspace which marked the site of an incision which had been made for empyema. An *x*-ray examination revealed about one-half of the stomach in the chest. A remarkable feature of this case is that, after cleaning up the sinus and irrigating with Dakin's solution, a gradual improvement occurred with a complete subsidence of the digestive disturbances although part of the stomach remained in the thorax. The child was sent home to gain weight before carrying out an operation for the repair of the hernia (see Figs. 22 and 23). Some cases of congenital diaphragmatic hernia have probably been wrongly diagnosed as empyema and operation has been mistakenly performed for that.

Symptoms and Diagnosis.—The diagnosis of empyema depends ultimately on an exploratory aspiration. The aspirating syringe therefore is the most important means of diagnosis. If all suspicious cases of empyema were subjected to an *x*-ray examination and then to an exploratory aspiration, fewer cases would be diagnosed as unresolved pneumonia, and likewise there would be fewer cases of neglected empyema. Ordinarily, the diagnosis is more likely to be confusing in the streptococcal than in the pneumococcal cases. In the latter the empyema usually occurs *after* the pneumonia; but in the former, massive fluid exudates may, and generally do, occur early in the course of the pneumonia. The combination of pneumonia and exudate often makes a confusing diagnostic picture.

Pain is seldom a conspicuous feature of empyema, except in the initial stage, but local tenderness may be present, especially if the infection has begun to involve the chest wall. On inspection, in children especially, the affected side may appear to be bulging and full, and some restriction of motion during respiration will be observed. In some cases, however, the affected side appears to be flattened. This is particularly true in the late cases. The cardiac impulse may be seen to be displaced.

Dyspnea and cyanosis may be extreme, particularly in the streptococcal cases; spirometric readings show a diminished vital capacity as would be expected.

On palpation the vocal fremitus is usually diminished on the affected side, but this is not an invariable rule. The apex beat will often be found displaced; and in neglected cases there may be some edema of the chest wall.

Percussion reveals dulness or flatness over the fluid with a sense of increased resistance to the percussing finger. The exudate most often is present in largest amount at the base. The level of dulness is not changed much by shifting the position of the patient. Grocco's sign of paravertebral dulness is often present.

On auscultation, although usually the respiratory sounds are weak or entirely absent over the fluid, occasionally, and especially in children tubular breathing may be heard over the whole dull area. It is evident that this fact may often lead to a mistaken diagnosis of consolidation rather than fluid. Cavernous and amphoric breathing are sometimes heard. Vocal resonance is diminished or absent over the fluid and egophany is often present at about the upper level of the fluid. Whispered voice sounds are absent in cases of frank empyema although they may be heard in cases of simple effusion.

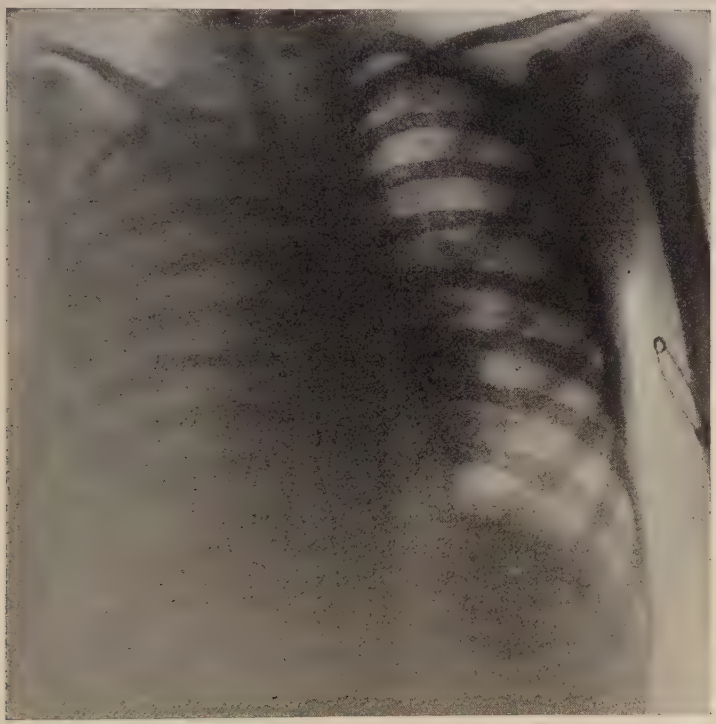


FIG. 24.—Skiagraph of empyema of left side with displacement of heart and other mediastinal structures to the right. (From St. Louis Children's Hospital.)

An *x*-ray examination is of the greatest importance. In cases of pleural effusion an obscurity shows instead of the normal clearness of the lung. Effusions at the base obliterate the angle normally present between the diaphragm and the chest wall (costophrenic angle). The heart and mediastinal structures are usually displaced somewhat to the side, especially in large effusions. Barjon[49] thinks that the combination of the obscurity of the normal lung clearness and the displacement of the mediastinum is practically pathognomonic of pleural effusion (Fig. 24, 25).

Special difficulties in diagnosis are presented by cases in which the effusion does not occupy the pleural cavity in the ordinary sense but

is encysted either between two lobes or elsewhere. Such cases are very likely to be confused with lung abscess. Because of a communication with the lung even the nature and amount of the sputum may suggest a lung abscess. In advanced cases of interlobar empyema, however, the diagnosis with the *x*-ray is usually easy. The distinguishing feature is an opaque zone or band which extends completely across one side of the thorax. Above and below are clear zones of lung. The width of the dark zone will of course be variable but its location in general corresponds to the position of an interlobar fissure.

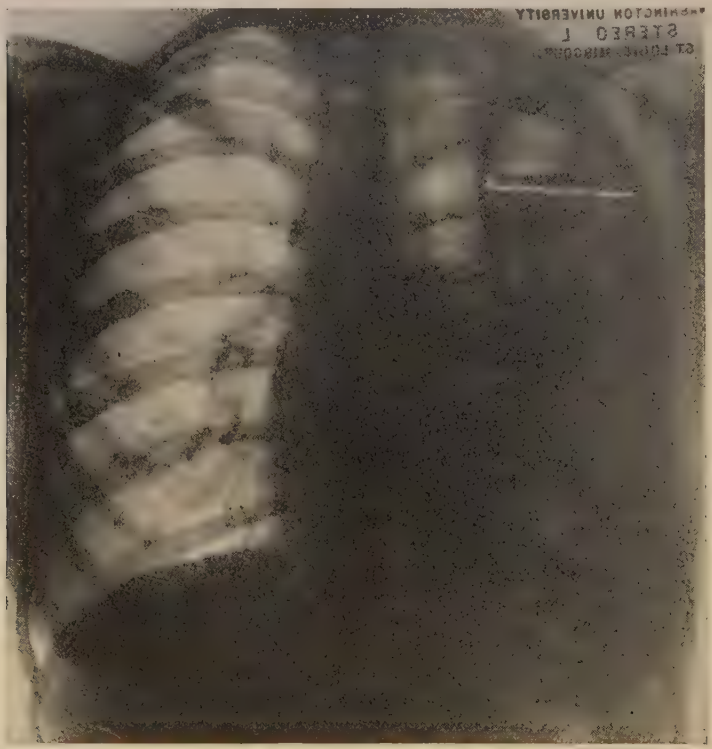


FIG. 25.—Skiagraph of pyopneumothorax due to hemolytic streptococcus from child 12 years old. (From St. Louis Children's Hospital.)

On the contrary, in lung abscess the shadow does not extend across the lung with such a definitely horizontal base, and it is often surrounded either totally, or at least on two or three sides, by a clear zone.

The temperature is subject to great variation. As in most febrile conditions, children are likely to have more fever than adults. But in chronic cases, and particularly in those that have been drained, the temperature may be practically normal. Temperatures of 104°F. or above almost always indicate the coexistence of pneumonia or of some complication with the empyema. When it exists, the fever is of the septic type with morning remissions. Actual chills are not

common in the usual uncomplicated case. The pulse is accelerated, and arrhythmia is common because of the frequency of myocarditis. A polymorphonuclear leukocytosis is almost always present; in children counts of 20,000 or more are not uncommon. A secondary anemia which may be extreme in some instances is practically the rule.

The constitutional disturbances do not differ essentially from those in any other severe febrile condition. Anorexia, emaciation, weakness and sweating may be conspicuous. Small amounts of albumin and a few casts are generally found in the urine. These ordinarily disappear quickly after adequate drainage has been established; but in the chronic cases, after amyloid changes have occurred, they may be permanent.

Clubbing of the fingers and toes (the pulmonary osteoarthropathy of Marie) is very commonly seen in the chronic cases. Although changes in the bone are sometimes detectable with the *x*-ray they do not seem commensurate with the amount of thickening of the soft parts. After the infection has become cleared up, the clubbing of the fingers and toes diminishes. A very exhaustive study of this condition has been made by Corper, Cosman, Gilmore and Black.[50]

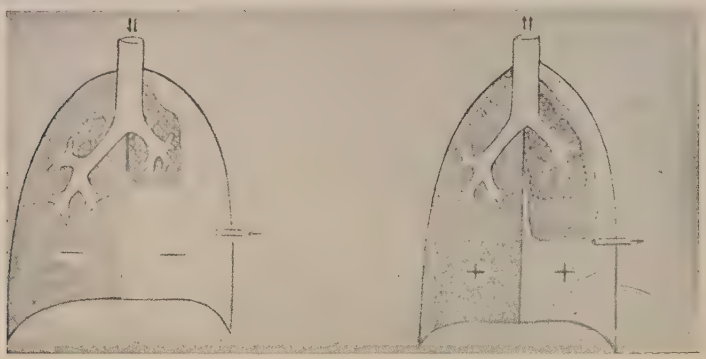
Treatment.—Physiologic Basis.*—In empyema, as in all other conditions a rational treatment must be based on correct physiologic principles. It is fitting, therefore, that the discussion of the treatment should be introduced by a consideration of the physiology volved.

The act of inspiration consists essentially of an enlargement of the thorax with a resultant inrush of air down the trachea and into the lungs in order to equalize the pressures of the air outside the body and inside the lungs. The act of expiration, on the contrary, is accomplished by a diminution of the thorax, which in turn forces the air out of the lungs. The amount of air, therefore, which is taken in and given out with each act of respiration, under normal conditions, is regulated almost entirely by the extent to which the thorax enlarges itself. The limit of possible enlargement is determined by a number of factors, important ones of which are the size of the individual, the flexibility of the thorax, and the strength of the respiratory muscles. Hence, it is evident that even so-called normal individuals may differ widely in their ability to enlarge the thorax, and those who have particularly strong respiratory muscles, athletes, for example, will show a greater ability in this direction than other individuals of the same size who have poorly developed respiratory muscles.

It is evident that in order to effect the inrush of air down the trachea the essential condition which must be created by the enlargement of the thorax is a diminution of pressure within the lungs. Under normal conditions the lungs are said to fill the pleural cavities completely.

* Since the completion of this manuscript in 1922, much of the theory of the action of pneumothorax which is briefly presented in this section has become the subject of controversy. The interested reader will find the whole matter brought up to date in my lecture before the Harvey Society of New York, February 9, 1924.

Actually they fill these spaces except for the presence of a very small amount of fluid which serves to moisten the two pleural surfaces. The elasticity of the lungs tends constantly to pull them away from the chest wall; and the cohesive force between the parietal and visceral layers of the pleura tends to hold the lungs in apposition to the chest wall. The result of the opposite directions in which the two forces are working creates a tension in the pleural space which is less than atmospheric pressure. It is obvious that if a record of the intrapleural pressure were made it would have its lowest value at the end of inspiration and its highest value at the end of expiration. Donders[51] was apparently the first to measure these pressures, at least in the human, and his values were −7.5 mm. Hg at the end of expiration and −9



a, Inspiration *b*, Active expiration

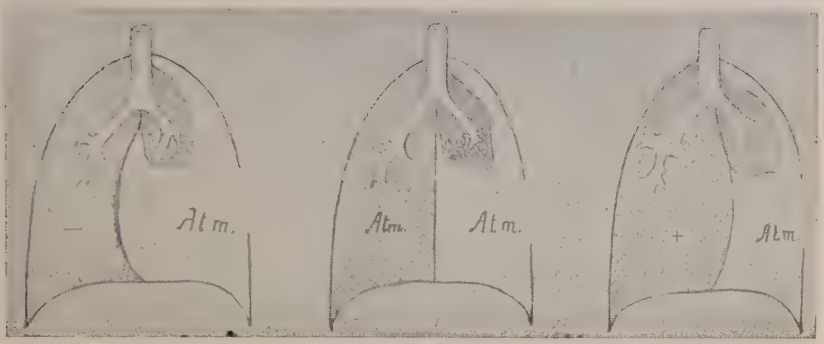
FIG. 26.—Respiratory mechanism in pneumothorax with small opening. (Garrè.)

mm. Hg at the end of inspiration. Aron,[52] in a living normal man, found an average pressure of −4.64 mm. Hg at the height of inspiration and −3.02 mm. at the end of expiration. More extensive reviews of these points may be found in the treatises of Emerson,[53] Sauerbruch[54] and L. Mayer.[55] If a tension less than atmospheric pressure cannot be established in the pleural cavity at some time during the inspiratory act, then air will not enter the lungs.

For these reasons it is of the greatest importance to consider both how the intrapleural tension may be altered and the effects of such changes. The most striking way to demonstrate the effects of suddenly altering it is to create an open pneumothorax.

The ordinary conceptions of the effects of an open pneumothorax have been based upon the faulty reasoning that any opening in the chest wall, no matter of what size, would result immediately in the establishment of atmospheric pressure within the pleural cavity on the side of the opening. They carry with them also the idea that the mediastinum acts as a more or less rigid partition between the two pleural cavities and that when an opening is made into one pleural cavity the lung on that side becomes collapsed and respiration is maintained by the other lung. These ideas have become so deeply

ingrained that all through the literature one finds references to the "collapsed" lung on one hand and the "sound" or "healthy" lung on the other. For example Garrè [56] in a series of diagrams to illustrate the conditions in open pneumothorax shows the mediastinum as a



a, Inspiration *b*, Normal expiration *c*, Forced expiration

FIG. 27.—Respiratory mechanism in pneumothorax with large opening. (Garrè.)

straight line, in cases in which the opening is small, with one lung collapsed and retracted and the other lung (on the unopened side) of normal size and apparently unaffected. In cases with a large opening essentially the same condition is shown except that there is a slight bulging of the mediastinum away from and towards the opening in

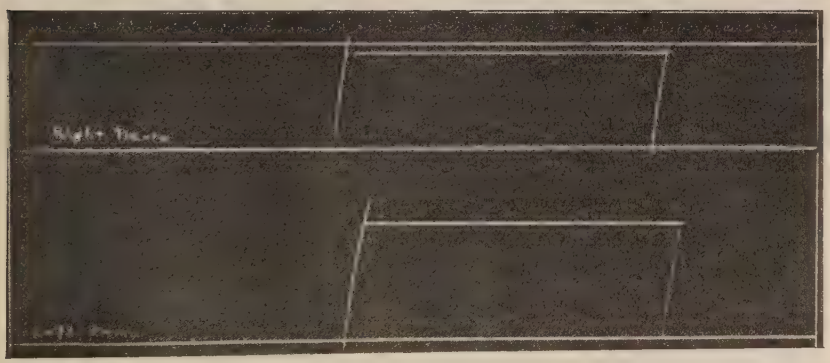


FIG. 28.—Tracing made from human body immediately after death and after inflation of the left pleural cavity with air to a pressure equivalent to 10 cm. of water. The recording needle in the right pleural cavity registers a pressure equivalent to 9 cm. of water. This shows that in the human body, when no adhesions or no thickening of the mediastinum is present, the resistance offered by the mediastinal structures is equivalent only to the pressure exerted by 1 cm. of water.

inspiration and expiration respectively. Likewise here also the lung on the side of the opening is shown as collapsed and contracted into a small mass about the hilum, whereas the opposite lung appears to be relatively unaffected (see Fig. 26, 27). L. Mayer[55] summarizes from

the literature the prevalent views on the changes produced by an open pneumothorax as follows: "On the healthy side the modifications due to the pneumothorax with a small opening should adjust themselves by a deviation of the mediastinal pleura, the two surfaces of which are

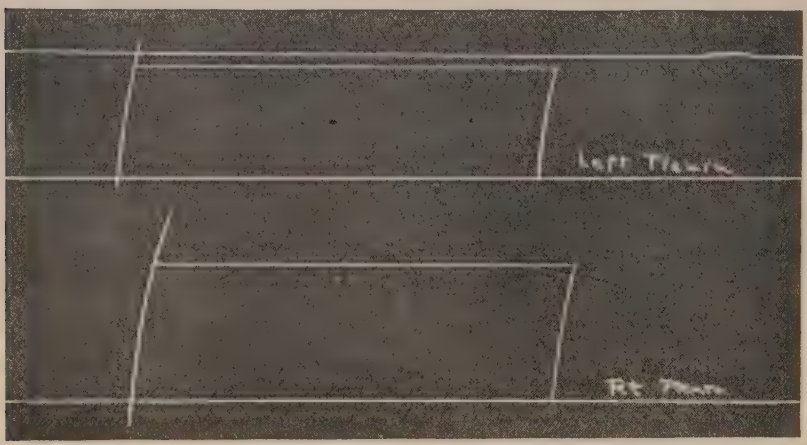


FIG. 29.—A similar tracing to that shown in Fig. 28, made with the right pleural cavity inflated. Calibration showed that in this case also there was a difference in pressure of only 1 cm. of water (about 0.8 mm. of mercury).

no longer submitted to conditions of identical equilibrium; on inspiration the lowering of intrapulmonary pressure of −7 mm. Hg. not manifesting itself on the fistula side, the mediastinal pleura should become curved towards the healthy side and narrow the expansion

FIG. 30.—Similar tracing to those shown in Figs. 28, 29 made on a dog immediately after death, which shows that the dog is strictly comparable with the human, since here also the difference in pressure between the two pleural cavities amounted to only 1 cm. of water.

of the other lung; the inverse should be produced at expiration. In reality these theoretical differences are minimal and are scarcely established by experimentation. If, on the contrary, the pleural opening is widely gaping the atmospheric air enters and goes out freely at each respiratory movement and the lung of this side will not be

called upon at all to become distended. At each inspiration the pressure of the two sides of the mediastinal pleura will be different; on the healthy side negative pressure of 7 mm. Hg, on the other side atmospheric pressure, with aspiration of the mediastinum towards the healthy side, towards which it ought to be markedly convex. In moderate and light expiration the pressure on the two sides remains equal; but if a forced or sudden expiration supervenes the pressure is raised in the normal lung while it remains constant on the incised side, giving a convexity of the mediastinum on the side of the pneumothorax."

Direct experimental observations which were made by R. D. Bell and the writer,[45] while members of the Empyema Commission of the U. S. Army, show that these conceptions are erroneous. If, for example, air is injected into one pleural cavity of a fresh human cadaver without adhesions, until a pressure of 10 cm. of water is obtained, the pressure in the opposite pleural cavity will register nearly the same, differing by only from 0.5 cm. to 2 cm. (see Figs. 28–30). This experiment shows that even with comparatively slight alteration of pressure the mediastinum is crowded over against the opposite lung. Whether this is accomplished by pulling or pushing is beside the point. With a greater alteration of pressure on one side, however, the agreement between the pressures of the two sides is not so close. Similar experiments made on the fresh human cadaver, in which there were no adhesions or induration of the mediastinum, and on the freshly killed normal dog yielded practically the same results. Accordingly it was felt that experimental results obtained on the living dog could be applied to the living human.

If, in the living dog, an open pneumothorax is created on one side, a characteristic response occurs which is manifested not only by a change of intrapleural pressure on the opened side but also by a change of the same kind and of practically the same degree on the unopened side. Briefly, the phenomena which occur are as follows: Immediately after making the opening there is a simultaneous change of pressure in the two pleural cavities from an entirely minus or negative (less than atmospheric) phase to one which oscillates between a positive or plus (more than atmospheric) and a minus phase. The size of the opening, as will be shown later, materially influences the extent of the change of pressure. The respirations are sometimes slowed and increased in amplitude, but at other times they are accelerated. As the intrapleural pressure diminishes, the intratracheal pressure tends to become constant, as would be expected, since the latter is a rough index of the amount of air passing down the trachea. Immediately upon closure of the opening there is a simultaneous response in both pleural cavities with a more complete restoration of negative pressure, diminution of the amplitude of the respiratory movements and oscillations again of negative and positive intratracheal pressure on inspiration and expiration. These changes can be better understood by reference to the reproduction of a tracing shown in Fig. 31.

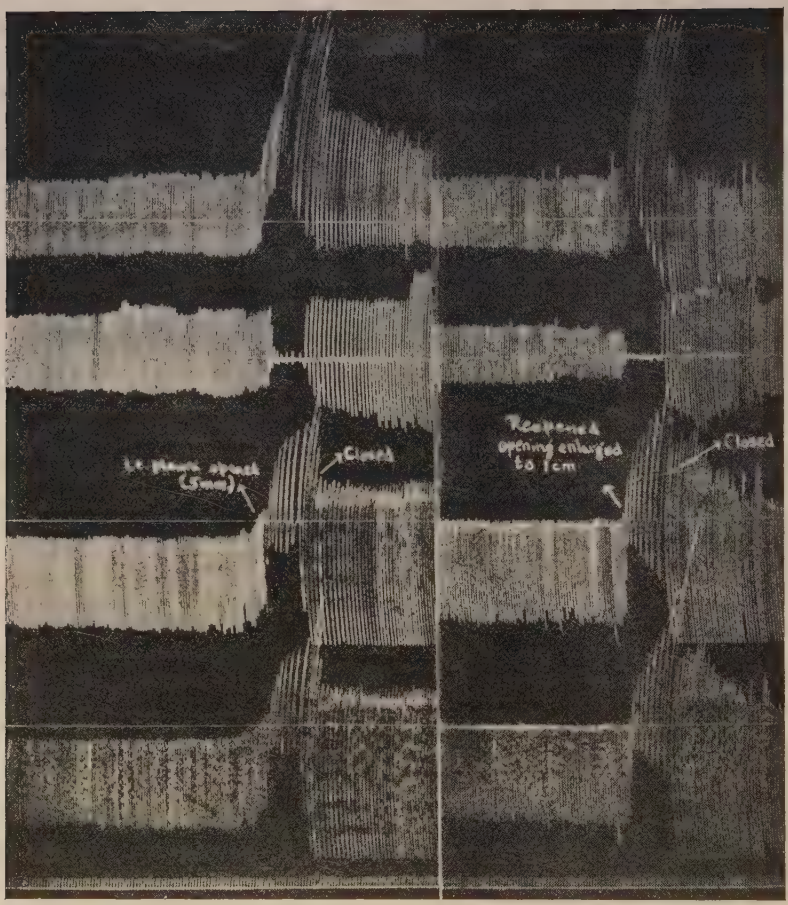


FIG. 31.—A tracing made on the living dog under ether anesthesia to show the nature of the reaction to an open pneumothorax with a moderate opening, as indicated in the changes in the respiratory movements, in the tracheal pressure and in the pressures in both pleural cavities. The upper tracing represents the respiratory movements, the next the tracheal pressure, the third the left pleural pressure and the fourth the right pleural pressure. The lowest line indicates the time in seconds. The base lines were drawn at atmospheric pressure. The interval represents a duration of six minutes. Immediately after making the opening there is a simultaneous change of pressure in the pleural cavities from an entirely negative phase to one which is mostly positive. The respirations are slowed but are increased in amplitude. Because the intrapleural pressure is largely positive, practically no air enters the trachea and the intratracheal pressure tends to be at equilibrium with atmospheric pressure. Immediately upon closure of the opening there is a simultaneous response in both pleural cavities with restoration of negative pressure to a large extent, diminution of the amplitude of the respiratory movements and oscillations again of positive and negative intratracheal pressure, with inspiration and expiration. After an interval of six minutes during which time part of the air in the pleural cavities has probably been absorbed the intrapleural pressure has again become entirely negative.

The extreme mobility of the human mediastinum in the absence of adhesions has been shown in *x*-ray studies on pneumothorax by Stivelman and Rosenblatt.[57] Their work tends to confirm the truth of the general idea here being developed of the practical equilibrium of pressure throughout the normal thorax. J. B. Murphy,[58] recognizing the dangerous tendency of the mediastinum to "flutter" in an open pneumothorax, recommended traction on the lung in an attempt to immobilize the mediastinum.

West[59] came to a conclusion which seems to agree rather closely with the idea of the practical equilibrium of pressure throughout the normal thorax which is being developed here. He apparently made no actual measurements of the pressures, but had he done so it would seem that his results would probably have been in exact agreement with ours. He states: "When one pleural cavity is laid freely open to the air there will then be atmospheric pressure on both sides of the visceral pleura; the elasticity of the lungs will come into play, and the exposed lung will collapse. But this is not all, for the alterations in pressure do not affect the one lung only; the mediastinum being not a fixed partition, but a movable one, the elasticity of the opposite lung also comes into play; with the result that the mediastinum and the organs therein are drawn over to the sound side. Thus it follows that the opening of one pleura not only satisfies the elasticity of the one lung, but goes a long way to satisfy the elasticity of the other. If, for example, the pressures be reduced to figures, and we assume for the sake of illustration that in a healthy man the total elastic contractility of the two lungs together amounts to 50, the opening of one pleura may satisfy this elasticity to the extent of 40, leaving only 10 for the unsatisfied elasticity of the opposite lung. Thus, in pneumothorax, which is the corresponding pathologic condition, if the lungs are healthy and their elasticity at its maximum, the total respiratory capacity will be suddenly reduced by four-fifths." Lenhart[60] has recently obtained results in experiments on rabbits which he says tend to confirm our previous results.

It should be stated here that often in small punctured wounds of the chest, even when the lung has been injured, the air does not enter the pleural cavity to create a pneumothorax but instead it finds its way into the soft tissues of the chest wall. This phenomenon is frequently seen in association with fractured ribs. As an explanation of it West[61] suggested that the cohesion between the two layers of pleura is so great that a considerable force is necessary to separate them. MacEwen[62] has also adopted this explanation.

The older conceptions of the immediate establishment of atmospheric pressure within a pleural space as soon as an open pneumothorax is created fail to take into consideration the fact that the thorax, instead of being a rigid box, has movable walls which, by varying the size of the contained space, also vary the pressure within it. If the older conceptions were correct, then a small opening into the chest would have the same consequences as a large one because in each case

"collapse" of the corresponding lung would occur. It would follow from this also that in a normal chest a unilateral open pneumothorax ought never to be fatal regardless of how large the opening might be, since the worst possible consequence would be the "collapse" of one lung. Similarly, also, with the same line of reasoning, a bilateral open pneumothorax should always be promptly fatal. Experiences, however, both experimental and in the war, which controvert these two conclusions, have been many. A dog, for example, will live indefinitely with a bilateral open pneumothorax, if the openings are not too large.

If any change of pressure in one pleural cavity were transmitted through the mediastinum to affect the other pleural cavity to exactly the same extent, then it would be possible to calculate, by means of a mathematical expression, approximately how large a pleural opening could be endured by any individual whose vital capacity* were known. As a matter of fact, however, the calculation shows a result actually too small, because when a great alteration of intrapleural pressure on one side is made, the pressure on the opposite side is not in very close agreement. However, the calculation is interesting in showing that, on theoretical grounds, it is not surprising that during the war it was found that men could withstand pleural openings of such great size that before the war they would have seemed impossible. The mathematical expression is as follows:

$$X = \frac{V - \frac{R_1}{R_2} T}{\frac{R_1}{R_2} T} aC$$

in which V is the vital capacity, R_1 is the rate of respiration before the opening is made, R_2 is the rate of respiration after the opening is made, T is the tidal air (approximately 500 c.c.), a is a factor less than 1 (assumed to be about 0.8), C is the area of the glottis (about 2.25 square cm.).

By substituting numerical values the determination of X becomes a problem of simple arithmetic. The average vital capacity V and the tidal air T are given by Howell[63] as 3700 c.c. and 500 c.c. respectively. The normal rate of respiration R_1 during complete rest is about 15 per minute and the maximum rate R_2 for the greatest possible depth of respiration is about 60 per minute.

$\frac{R^1}{R^2} T$ then equals 125 and

$$X = \frac{3700 - 125}{125} aC = 28.6aC$$

$$X = 28.6(0.8 \times 2.25) = 51.5 \text{ square cm.}$$

In other words in an individual with an average "vital capacity" (3700 c.c.) an opening of about 51.5 square cm. (8.1 sq. in.) is the largest for which compensation can be made if the mediastinum has a

* Vital capacity is a term used by physiologists to represent the maximal amount of air which can be expired after a maximal inspiration.

normal mobility. It is obvious, however, that when the factor V ("vital capacity") is increased the value of X will also increase. Consequently those individuals whose "vital capacities" are greater than 3700 c.c. will be able to withstand openings of greater areas than 51.5 square cm. In this connection it is noteworthy that Peabody and Wentworth[64] have shown that the average vital capacity for men is considerably higher than that of the general average of both men and women. The average value based on their observations on men is 4633 c.c. If we substitute this value for V in our equation we find a value for X of 64.8 square cm. (10 sq. in.). The maximum opening therefore for which the average man can compensate is about 64.8 square cm. In the exceptionally large man of athletic build, as for example, in the case of the man mentioned by Peabody and Wentworth[64] who had a "vital capacity" of 7180 c.c., a relatively enormous opening in the chest wall can be compensated for. In such a case, for instance, the value of X in our equation would be 101.3 square cm., or 15.6 sq. in. Practically, the opening must be somewhat smaller, since the extra work performed by the muscles of respiration to establish compensation increases the amount of air required. The presence of toxemia, infection or any other cause which increases the level of metabolism will decrease the safety limits of the maximum size of the opening, as will also any condition reducing the available breathing space of the lung. The use of general anesthesia will probably also act in the same way. It should be borne in mind that the value of X represents the approximate maximum opening compatible with life only so long as the respiratory muscles can maintain a maximum respiratory movement, and in addition, that it is only an approximation because of variability in different individuals of some of the other factors, as for example, C.

The reasons for this quantitative relationship are to be found in the facts that: (1) It is possible to maintain life as long as the lungs can inspire the "tidal air," which normally is from 300 c.c. to 500 c.c.; (2) a considerable encroachment on the volume of the two lungs can be made before a stage is reached at which it is no longer possible for the lungs to obtain the "tidal air;" (3) in the compensatory reaction, by an increase in the amplitude of the respiratory movements the thorax is enlarged so that actually more air may enter through the pneumothorax opening without encroaching on the "tidal air" to the same extent than would be the case if the thorax were not enlarged.

It must be particularly emphasized, however, that this consideration refers only to the normal thorax. Obviously, a thickening of the mediastinum by old inflammation and the presence of strong adhesions will change the conditions and will permit the development of a very great pressure on one side with perhaps no alteration of pressure on the other side.

In addition to its effects on respiration, an open pneumothorax also induces other harmful effects. These have been summarized by Sauerbruch as loss of heat, danger of infection and disturbances of the

circulation. He has made the important observation that the loss of heat from an open pneumothorax may exceed that which follows an extensive laparotomy incision with eventration of the intestine. Also, owing to the changed pressure relationships, a stasis in the venous system occurs which is shown by an actual increase of pressure in the femoral vein.

In the case of a closed pneumothorax very different conditions from those in an open pneumothorax are present. In the description of the characteristic changes produced by making a free opening into the pleural cavity it was stated that the closure of the opening resulted in a sudden restoration of negative pleural pressure and a prompt relief from dyspnea. Obviously, after making the closure, air is still retained in the pleural cavity, so that the very striking difference in the phenomena observed must be due merely to the fact that an open pneumothorax has been converted into a closed one. Although air is absorbed from the pleural cavity, it disappears only slowly; and the sudden benefit noted by the closure of the opening cannot be attributed to the immediate disappearance of the air. Apparently the explanation of the relative harmlessness of a closed, in comparison with an open, pneumothorax lies rather in the fact that the ability to compensate for interference with the aëration of the lungs is limited. In a closed pneumothorax, no matter how much air is contained in a pleural cavity, no additional air can enter. It is necessary, therefore, only for the animal to increase his respiratory effort sufficiently to create enough negative pressure to allow him to take in the requisite amount of air to maintain oxygenation of his blood. Under conditions of rest this amount is equivalent only to the "tidal air," which in the human is only a relatively small fraction of the "vital capacity" (from about one-seventh to one-twelfth). Accordingly, therefore, a fatal asphyxia should not occur until so large a proportion of the lung capacity has been replaced by air in the pleural cavity that his "vital capacity" equals his "tidal air," provided that the animal is at rest, that his ability to compensate by increasing his respiratory effort is good and that there is no extra abnormal demand for air such as might arise from toxemia. When an open pneumothorax is converted into a closed one, particularly if the closure is made at the end of expiration, the amount of air enclosed in the pleural cavity is very much less than the normal difference between the "tidal air" and "vital capacity," and naturally, therefore, there is comparatively little dyspnea. On the other hand, in the case of an open pneumothorax there is an active competition for air going on between the trachea and the pleural opening. At each inspiration air not only enters the trachea but also enters the pleural cavity, and if the diameter of the pleural opening is the same as that of the glottis, practically the same amount of air will enter the pleural cavity as will enter the lungs and the animal will be compelled to increase his respiratory effort to get the "tidal air" into his lungs. If the opening is considerably larger than the glottis it will be still more difficult to get the required amount of air into the lungs.

When it is so large that more air than the difference between the "tidal air" and the original "vital capacity" enters the pleural cavity with each inspiration, the animal will no longer be able to obtain the requisite "tidal air" and death from asphyxia will occur. This theoretical discussion is of course only an approximation and is not strictly accurate, since it is necessary to consider the actual amount of air entering by each opening rather than merely the differences in area, a consideration which involves also the relative lengths of the pleural opening and the trachea with the resultant friction to the passage of the air. Observations, however, both clinical and experimental, tend to confirm the truth of this explanation. Clinically, it is well known that an individual of average size may have no alarming dyspnea from a pleural exudate amounting to 2000 c.c. or 2500 c.c. Exudates greater than this, however, frequently produce very severe dyspnea, particularly if the respiratory muscles are weak. Experimentally, we have injected into the pleural cavity of a dog of 8 kg., through a small needle, as much as 1800 c.c. of air over an interval of 20 minutes without producing any marked asphyxia. Beyond that point, however, additional injections of only 50 c.c. at a time each had a very noticeable effect in increasing the dyspnea, and the animal died after about 2100 c.c. of air had been injected.

The considerations of the effects of pneumothorax discussed above receive clinical confirmation from the experience in the war with wounds of the chest. Reference has already been made in another section to the fact that army surgeons found not only that surprisingly large gaping wounds of the thoracic wall did not necessarily result in a fatal asphyxia but also that bilateral "sucking" wounds were not inevitably fatal. These findings are easily explained, however, by the quantitative relationship between the size of the opening, the "vital capacity" and the other factors mentioned above in this connection. For it has been shown, on the basis of our calculations, that an average normal man, even without adhesions, and even if the mediastinum offered no resistance at all, could compensate for an opening of about 64.8 square cm. (10 sq. in.) until his respiratory muscles became fatigued or unless his need of oxygen became abnormally great. But because the mediastinum does offer a good deal of resistance, to great alterations of intrapleural pressure, the maximum nonfatal opening in the average man would be considerably larger than the value given. Practically, in operative procedures on the chest, measures are always adopted by the operator to reduce the size of the opening. One which is apparently very large is often actually much smaller, because of the presence in the incision of a lung which has been delivered out, gauze sponges, instruments, and fingers of the operator or of his assistants, all of which by their plugging tend to reduce the area of the opening. Also, the delivery of the lung outside of the chest wall accomplishes to some extent the immobilization of the mediastinum. There is, therefore, apparently a perfect harmony between the conceptions of pneumothorax based on the above

experimental results and the clinical observations on wounds of the thorax.

Principles and Methods of Treatment.—Although empyema was known to the ancients and the importance of drainage was recognized by Hippocrates, there are few surgical conditions which have aroused more discussion during the last 50 years concerning methods of treatment. This fact of course signifies strongly that no method has given results which could be considered as satisfactory, because with each the mortality has seemed to be higher than the condition warranted. The epidemic of hemolytic streptococcal infections of the respiratory tract associated with empyema which ravaged the military camps of this country during the winter of 1917–18 did much to clarify the general understanding of not only the pathology but also the treatment. As a result of this opportunity of studying intensively and under proper control a very large number of cases, certain principles have come into general recognition which, although most of them are not new, have resulted in the establishment of more or less standard methods of treatment. In this respect the situation in regard to empyema has undergone much of the same transition as did the question of the treatment of appendicitis a few years ago in that now certain clearly established principles seem to warrant some degree of standardization of treatment.

The principles which seem now to be established in the treatment of empyema are: (1) Drainage, but with the careful avoidance of an open pneumothorax during the period of active pneumonia; (2) early sterilization and obliteration of the cavity; and (3) maintenance of the nutrition of the patient.

Drainage with Avoidance of Open Pneumothorax during Pneumonic Stage.—In the light of what has been said above concerning the pathology and the physiologic basis of treatment, it is obvious that if an open pneumothorax is created by establishing drainage in a patient who is already partly asphyxiated, such a serious burden may be added to him that he will succumb. He will certainly die if enough interference with his breathing exists to make his "vital capacity" equal his "tidal air;" for under such circumstances he will not be able to tolerate even a tiny opening in his chest.* Undoubtedly many lives have been sacrificed because of ignorance of this principle. When the Empyema Commission[65] substituted at Camp Lee, in place of an early open operation, a method of repeated aspirations during the pneumonic stage with a deferred drainage operation, the mortality dropped from a little more than 40 per cent. to 4.3 per cent. Similar striking reductions in the mortality occurred in other camps when early open drainage was abandoned. In a valuable statistical article Stone[47] has shown the marked reduction in mortality which occurred at Fort

* The partial asphyxia which is most dangerous in cases of empyema is that type which is due to an active pneumonia. This is usually associated with cyanosis. There is of course always some dyspnea in cases with large pleural effusions which usually improves promptly after the evacuation of the fluid.

Riley, Kansas, after the early open operation was abandoned. His cases are divided into three series and the following quotation from his article will reveal the striking difference in mortality:

"1. First series: Early operation (Oct. 20, 1917, to Jan. 21, 1918), 85 cases. Mortality, 61.2 per cent.

"2. Second series: Early aspirations and late operation (Jan. 12, 1918, to Aug. 10, 1918), 96 cases. Mortality, 15.6 per cent.

"3. Third series: Early aspirations and late operation (Oct. 18, 1918, to Feb. 14, 1919), 94 cases. Mortality, 9.5 per cent."

Souligoux,[66] who advises early open drainage in all cases of acute empyema, states that the mortality of the streptococcal cases is never less than 25 per cent., a conclusion which seems to me to be significant in the light of the much lower mortality obtained in the American army when an early open drainage was not performed. In addition to the danger of an open pneumothorax there are certain other dangers inherent in even so minor an operation as the establishment of drainage. One of these is the possible creation of a septicemia. It is felt that this danger exists particularly in the streptococcal cases. In fact at Camp Lee in several instances we found a positive blood culture of streptococci shortly after operation in patients whose blood immediately before operation was sterile. The operations referred to were both simple intercostal incisions and rib resections performed early during the pneumonic stage of the empyema. The fact that positive blood cultures were very uncommon in other cases made us feel that doubtless some definite relationship existed between the early operation and the creation of a septicemia. This seems all the more likely when one recalls that a very close analogy exists between these streptococcal infections of the lungs and pleura and the ordinary streptococcal cellulitis cases which occur in other parts of the body. Experience has clearly shown in the case of the latter that free incisions during the acute stage aggravate the condition.

There are two ways by which at least some drainage can be accomplished without creating an open pneumothorax. One of these consists of repeated aspirations to be followed later by open drainage, and the other of the establishment of continuous closed drainage by means of a tightly fitting tube so arranged as to exclude air. Both aspiration and continuous closed drainage are old methods. Although each has had its enthusiastic advocates from time to time, neither method exclusively has given satisfactory results.

In 1844, before the Royal Medical and Chirurgical Society of London, Hamilton Roe[67] advocated aspiration as a therapeutic measure in empyema. He reported nine cases of purulent effusion in which eight were said to have recovered and one died. Of 39 cases of pleural effusion of all kinds which had been reported in British medical journals between 1812 and 1842 as having been treated with aspiration, only 11 were fatal. He emphasized the importance of early paracentesis, not later than three weeks from the outset. At the same meeting Theophilus Thompson reported recovery in a case of empyema

in a child upon whom he had performed repeated paracentesis in the preceding summer, carefully excluding the entrance of air by tying "thin skin" over the end of the cannula during the procedure. In this country Henry I. Bowditch[68] was one of the first to employ paracentesis in pleural effusions of all kinds, and it was largely owing to his enthusiastic advocacy of the method that it became popular in America. He gave credit to Dr. Morrill Wyman of Cambridge, Mass., for the invention of the aspirating device which he used successfully on several cases.

A small percentage ofcases of empyema will recover after aspiration alone, a few after a single aspiration, more after repeated ones. The method is not to be relied upon, however, and when used it should be only as a temporary procedure for the purpose of tiding a patient over the acute pneumonic stage of the illness, with the expectation of establishing adequate drainage later if necessary. Of the acute cases studied by the Empyema Commission, 13 per cent. recovered after aspiration alone. This agrees closely with Stone's[47] finding that at Fort Riley 11.3 per cent. recovered. Holt[69] says that in 139 cases of children treated by aspiration, 25 recovered (18 per cent.), 8 of these by a single aspiration; 13 died (9.3 per cent.) and the remaining 101 were afterwards subjected to other treatment. Objections to the method of aspiration alone are (1) the difficulty of providing in this way adequate drainage because of the presence in the exudate of masses of fibrin and necrotic tissue which are too large to pass out through a needle or trocar, (2) possible harm resulting from the puncture of the lung or a blood-vessel with the needle, or from pleural reflexes, and (3) the incontrovertible fact that most cases which have been treated by aspiration alone require a drainage operation later.

To perform paracentesis a method should be used which does not permit the entrance of air into the pleural cavity. For this purpose the Potain[70] aspirator is well adapted. The needle should be inserted in an intercostal space at the lower portion of the fluid. In most cases the site of election is in the eighth interspace in the posterior axillary line. The procedure can easily be made painless, or practically so, even for young children by an intelligent use of local anesthesia. To accomplish this it is important that not only should the skin and subcutaneous tissues be anesthetized but also the parietal pleura. One-half per cent. novocain is advantageous for this purpose. For the aspiration the child should be in a comfortable position. It is not necessary that he should be in any particular position. The fluid should be withdrawn slowly, and the aspiration may be continued until either no more fluid is obtained or untoward symptoms supervene. Capps and Lewis[71] have shown experimentally in dogs that irritation of an inflamed pleura frequently leads to a collapse with a sudden drop of blood-pressure similar to the syncope sometimes observed in the human during aspiration or irrigation of the pleural cavity. They found that artificial respiration was the most effective means of restoring the blood-pressure.

If a method of repeated aspirations is to be carried out, the process can be repeated as soon as any considerable reaccumulation of exudate occurs. In the army epidemic we found that usually it was desirable to repeat the aspiration in from four to six days. If repeated aspirations are made, the appearance of the fluid will change. Whereas at first, in a streptococcal case for example, it was sero-fibrinous, slightly blood tinged and thin enough to pass through the aspirating needle without much difficulty, it will gradually become thicker and more frankly purulent, assuming at the same time a slightly greenish tinge. If the aspirations have been made at intervals of three or four days, usually by the third or fourth aspiration it will be definitely frank pus. As a rule also, coincident with the change in the character of the fluid, a general improvement in the patient's condition will have been noted, as shown by a diminution in the fever, the disappearance of cyanosis and extreme dyspnea, a better quality of the pulse and an increase in the appetite. Frequently the path of the needle becomes infected, and occasionally an abscess forms in the soft parts.

Continuous drainage by a "closed" method, that is, one which does not permit the entrance of air to the pleura, is also an old practice, although as Binnie[72] says "in recent years it has been frequently rediscovered and modified in unessential details." One of the first enthusiastic advocates of it was Cresswell Hewett[73] in 1876, who described his plan of "continuous aspiration" as follows: "Paracentesis being performed with an ordinary trocar and canula, a caoutchouc (rubber) tube is placed through the canula into the empyema cavity; the canula is then extracted, and the outer end of the caoutchouc tube is attached to a glass tube, piercing the cork and reaching to the bottom of the vessel containing a weak solution of Condy's fluid or antiseptic. By gently lowering and raising the bottle the cavity is washed out, and by changing the first bottle for another and similar one, the cavity is evacuated of pus, and filled with antiseptic solution; thus the pressure on the vessels in the wall of the sac is not much, if at all, altered, and hemorrhage and transudation are prevented. The amount of fluid to remain in the cavity is lessened day by day, by increasing the siphon action of the apparatus by keeping the bottle at a lower level each day than the day previous." Bülau[74] in 1891 proposed a method almost identical except that he recommended irrigations with lime-water through the tube. Since that time the principle of suction drainage has been generally, and particularly in this country, credited to Bülau although Hewett had antedated him by 15 years. During the war the principle was extensively revived again in the United States army camps and subjected to modifications to such an extent that almost every camp had its own pet scheme for continuous suction drainage, for each of which the enthusiastic advocates made claims of vast superiority over all other methods, often with a vehemence which approached the acrimony of a theological discussion.

Mozingo[75] has been one of the most enthusiastic of the recent advocates of the principle of closed drainage. For the details of his

treatment reference should be made to his article. He combines a system of closed drainage with irrigations of Dakin's solution and Murphy's fluid (2 per cent. liquor formaldehyd in glycerin). Diederich and McKenna[76] had employed a method very similar to Mozingo's at Camp Pike before his arrival there. Mozingo reports a series of 138 cases, 45 acute and 93 chronic, treated by himself, with a mortality of less than 2 per cent. He regards an open drainage operation as practically never necessary and states that he has not found it necessary in his series of cases. It does not seem likely that an exclusively closed method could have such uniformly good results unless particularly favorable conditions were present, such as diminished virulence, etc. As a matter of fact Moschcowitz re-examined and found pus in a number of patients at the Walter Reed Hospital whom Mozingo is said to have pronounced healed. Holt[77] advocates with enthusiasm suction drainage over other methods for young children. The method employed was devised by J. H. Kenyon. A catheter (27 French) is inserted between the ribs and connected with another tube which passes into a bottle containing sterile salt solution. The comparative table, however, which he gives does not show any striking difference between any two of the methods stated:

Years	Simple incision, recovered	Died	Mortality, per cent.
First	3	13	81
Second	10	11	52
Over two	6	3	33
	Rib resection		
First	2	7	77
Second	11	11	50
Over two	3	0	0
	Siphon drainage, recovered	Died	Mortality, per cent.
First	8	12	60
Second	6	11	64
Over two	8	1	11

It is a striking fact, which is again brought out by the foregoing tabulation, that empyema in children under two years of age has always had a very grave prognosis.

Theoretically, the early establishment of continuous drainage with negative pressure should have the advantages of keeping the pleural cavity relatively free from liquid exudate and organisms, of aiding the expansion of the lungs as well as of avoiding an open pneumothorax with its attendant dangers. Practically, however, it seems doubtful if the results are appreciably better than with the method of repeated

aspirations. There is also the additional risk, slight though it may be, that a delirious and unmanageable patient may, by interference with the apparatus or the drainage tube, allow air to enter his pleural cavity and may suffer from the effects of an open pneumothorax before it can be corrected. This danger was one of the considerations

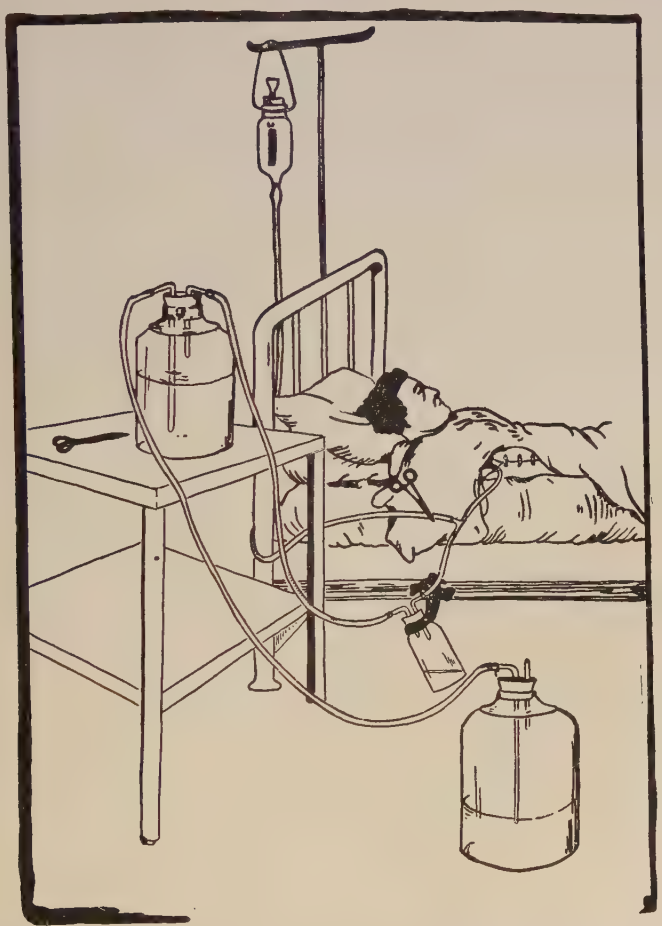


FIG. 32.—Diagram of closed drainage device as used by the Empyema Commission, U. S. Army. It also permits irrigation as often as desired. (Devised by Moschcowitz.)

which deterred the Empyema Commission from adopting as a routine the early establishment of continuous drainage with negative pressure, although in some cases it was used (see Fig. 32).

Regardless, however, of whether a method of repeated aspirations or of continuous closed drainage is used to tide the patient over the acute pneumonic stage, it seems to me that every case should be

regarded as one in which an operation for the creation of free drainage will be necessary at the proper time. It should be regarded as exceptional for a case of empyema not to require free drainage. If the exudate clears up under the conservative treatment and does not return, operation may be withheld; but the patient should be under close observation for at least a month.

Aside from the danger of creating by an early operation an open pneumothorax with its attendant harm during the pneumonic stage, there are also certain other advantages in a deferred operation: (1) By the time the pneumonia has subsided and the exudate has become frankly purulent, a more or less diffuse cellulitis of the pleura has become converted into an abscess shut off by adhesions from the rest of the pleural cavity. An operation at this stage not only minimizes, therefore, the risk of creating an open pneumothorax because it is not necessary to open into the free pleural cavity, but it presents the safer aspect, well known to surgeons, which the drainage of a streptococcus abscess always has over premature incisions into cases of cellulitis before an abscess has formed. (2) Even if an open pneumothorax should by chance be created, the patient is in a much better condition to withstand its harmful effects, because (*a*) the subsidence of the active pneumonia has the effect of making the area of the air-inlet to the lungs larger than when many of the bronchioles and much of the lung parenchyma are blocked by the pneumonic process, so that the pleural opening is incapable of producing the same amount of harm, (*b*) the presence of adhesions and the inflammatory thickening and induration of the mediastinum tend to make it less mobile, (*c*) the patient's need of oxygen is less because of a more nearly normal metabolism, (*d*) the respiratory compensation is more efficient since, owing to a diminished toxemia, the respiratory muscles will not become so easily fatigued.

The danger of early open operation has recently been recognized by Legendre[78] who divides patients with empyema into two classes: (1) Those with "white dyspnea" in whom the dyspnea is moderate, the respiration rate being about 25 to 30 per minute. The pallor is due to toxemia. The pulmonary lesions are either extinct or are nearly well. In such cases a considerable time has elapsed since the beginning of the infection. After operation the fever subsides promptly, the dyspnea improves progressively, and recovery is the rule. (2) Those with "blue dyspnea" in whom the rate of respiration is from 45 to 50. There is marked cyanosis of the face and extremities. These symptoms are in proportion to the pulmonary and not the pleural lesions. Operation increases the dyspnea, has no effect on the fever and is generally promptly followed by death. Wilensky,[38] also, gives the following tabulation in his article which seems to illustrate rather forcibly the increased mortality in operations performed too early in the course of the disease; the final column, showing the percentage mortality, has been calculated and added by myself:

DURATION BEFORE OPERATION

Time	Cases	Deaths	Mortality, per cent.
Under one week	57	27	47
1 to 2 weeks	91	24	26
2 to 3 weeks	46	10	22
3 to 4 weeks	31	7	22
4 to 5 weeks	18	3	16
5 to 6 weeks	9	1	11
7 to 8 weeks	13	1	7
2 to 3 months	17	3	
3 to 4 months	12	4	
4 to 5 months	3	2	
1 year	1		
2 years	1		

The cases upon which the foregoing tabulation is based were from civil life and included all sorts of empyemata. The delay in operating was not intentional but was due supposedly chiefly to a failure of the patient to present himself for examination at an earlier period. During the delay nothing had been done, not even aspirations. Presumably the difference would have been still more striking if repeated aspirations or a continuous closed drainage had been instituted. Werner[79] also has noted a lower mortality in cases in which drainage was not instituted until a considerable time after the onset of the empyema. These observations are not meant to imply of course that, because the mortality happened to be lower in the eighth week, all cases of empyema should be allowed to go until that time before operation. It is probable that if a large series of cases could be seen from the outset in which intentional neglect for eight weeks was carried out, the mortality would be higher than shown in this table. Only the survivors were able to present themselves for operation. The observations do, however, tend to show that an empyema rarely, if ever, requires an emergency operation. It seems to me that the former custom of rushing a patient with an acute empyema to the operating room for drainage as soon as it is recognized has been incontrovertibly shown to be irrational and positively harmful in the vast majority of cases. The only aspect of an acute empyema which may require an immediate interference for relief is the presence of alarming or distressing dyspnea. The only type of dyspnea which may arise which is amenable to relief by intervention is that which is induced by an excessive pressure within the thorax. This may be the result of either an excessive amount of fluid exudate alone or of a combination of a spontaneous, rapid accumulation of air within the pleura in addition to the fluid. In either case prompt relief can almost invariably be given by aspiration.

Pneumococcal empyema differs considerably from streptococcal empyema in the fact that ordinarily it is not recognized until after the

subsidence of the pneumonia. In this sense it is "metapneumonic" as suggested by Gerhardt.[80] As soon as it is recognized, therefore, many of the conditions are usually present which we strive to accomplish in the streptococcal cases by the preliminary aspirations. Doubtless it is mainly for this reason that formerly, when early open drainage was extensively practised in empyema, the mortality in the pneumococcal cases was generally much lower than in those due to the streptococcus.

These considerations lead us up to the pertinent question of when should an operation for drainage be performed in a case in which the patient has had a preliminary treatment with aspirations or continuous closed drainage. There can be no hard and fast rule about this. When the exudate has lost its serofibrinous nature and has become frankly purulent, operation may safely be performed. This usually indicates that the pneumonia has subsided and that adhesions have formed to wall off the abscess. Ordinarily three or four aspirations are performed during the course of from 10 days to two weeks. This was the plan which we carried out with the Empyema Commission, and the same line of treatment during the last two years at the St. Louis Children's Hospital has given extremely satisfactory results.

Between September, 1919, and September, 1921, during which time it has been customary to avoid an open pneumothorax in the acute pneumonic stage, there were 41 children in the St. Louis Children's Hospital on whom a diagnosis of empyema was made. In four of this number the empyema was not recognized until necropsy, and it was thought by the pathologists to be merely a terminal incident of other serious conditions. The principal diagnoses, for example, in these four cases were (1) foreign body in esophagus, perforation of the cardiac end of the stomach with extensive peritonitis and suppurative mediastinitis, (2) thrombosis of cavernous sinus, brain abscess, cerebrospinal meningitis, pan-sinusitis, staphylococcus aureus septicemia, (3) generalized acute streptococcal peritonitis secondary to appendicitis, (4) chronic interstitial nephritis with anasarca. In addition to the four patients just mentioned there were three others who were dying when brought into the hospital and who lived less than twenty-four hours after admission. One of these was aspirated just a few minutes before death but nothing was done to the other two. There were, in addition, four other deaths in patients who were treated in accordance with the principles discussed above. If the seven patients who received no treatment are excluded from the series, there will be then 34 cases of empyema and four deaths, a mortality of 11 per cent. This compares favorably with that cited above by Wilensky who shows in a total of 200 cases in children up to 10 years of age, 57 deaths, a mortality of 28 per cent. It also bears comparison with the tabulation quoted from Holt in which a grand total of 126 cases is shown with 69 deaths, a mortality of 54 per cent.

Statistics, however, as everyone knows, are very unreliable criteria from which to draw conclusions unless the differences are very

striking. It seems to me, however, that the figures presented here are sufficiently striking to show that, at least from the standpoint of mortality, the method of repeated aspirations to be followed by free open drainage is one which is not to be feared and which may prove to give the best results. The results are perhaps still more striking in the case of infants. It is well known that empyema in children under two years is always accompanied by a very high mortality. In Wilensky's[38] statistics it is given as 21 per cent. and in Holt's[41] it is found to be 64 per cent. if an average is made. In our series there were 12 patients under two years of age and two deaths, a mortality of 16 per cent. One of these deaths, however, could not possibly be ascribed to empyema because the child had practically recovered from his empyema. He entered the hospital on January 16 with scarlet fever. On February 11 fluid was recognized in the left chest, and 250 c.c. of serofibrinous fluid were aspirated. On February 14 and 17 he was aspirated again with the withdrawal each time of approximately the same amount of fluid (200 to 250 c.c.) which, however, was distinctly purulent on February 17. On February 18 a rib resection was made and 200 c.c. of streptococcal pus were removed. The cavity became rapidly sterile and obliterated. On March 12 its capacity was only 8 c.c. and on March 24 there was only a short sinus still unhealed. He was eating well, gaining weight and was playful. He was transferred to medicine. On April 18 his temperature was elevated and a paracentesis of his right ear drum evacuated a considerable amount of foul pus. On April 19 the left upper lobe showed pneumonic findings. Death occurred on April 26. No reaccumulation of fluid occurred in chest. Necropsy permission was not granted. It seems hardly possible, therefore, that the death could be ascribed to empyema, although I have included it here because the lack of necropsy creates some uncertainty about the condition.

The operation which we usually employ on children is the subperiosteal resection of about 1 in. of a rib. As a rule it is performed with novocain anesthesia; occasionally, if the child is badly frightened, nitrous oxid and oxygen are used. The particular rib selected for resection depends considerably, of course, upon the location of the empyemic abscess. A rib at the lowest portion of the abscess will ordinarily be chosen, but never one lower than the ninth because of the danger of injury to the diaphragm. Most commonly the eighth or ninth rib in the posterior axillary line is the one selected. Anterior drainage is never done except in the unusual cases in which the abscess is immediately behind the anterior wall. Chevrier[81] found on the cadaver that resection of the sixth rib in the posterior axillary line permitted the retention of 650 c.c. of fluid in the recumbent posture and from 1250 to 1300 c.c. in the erect; while the resection of the eighth rib in the scapular line caused retention of 300 c.c. in the recumbent posture and from 150 to 200 c.c. in the erect. Observations on the cadaver, however, are not entirely applicable to the living, because after death the cessation of respiratory movements does away

to a great extent with the power of the thorax to empty itself. The movement of the diaphragm must be important in this respect. Binnie[72] states that an opening made at the angle of the seventh, eighth or ninth rib will drain the cavity absolutely when the body is recumbent.

After making the rib resection it is advisable to have the patient cough or strain a little. This procedure will frequently force up into the opening large masses of fibrin, sometimes as large as the palm of the hand, which, if retained, delay healing, but which by this method can usually be easily recognized and removed at the time of the operation. By digital exploration also, or by use of an endoscope, large masses may sometimes be recognized which fail to appear merely by coughing or straining. Some surgeons attempt also to break up adhesions with the finger. I feel myself that that is a practice which should be strongly condemned, for much the same reasons that no one would think of similarly breaking up the adhesions around an abdominal abscess. One of the objects in deferring the operation is to localize the infection into an abscess. Why then disseminate the infection again? I feel also that the practice of attempting decortication in an operation for acute empyema is most unwise and will certainly do more harm than good in most cases.

In our own practice usually two rubber tubes, which are bevelled at the end and fenestrated, are passed into the cavity and anchored on the outside with safety-pins. Preferably these should be of fairly stiff rubber (not soft enough to collapse of themselves) and with an inside lumen of about a half inch in diameter. In babies it will be necessary to use smaller tubes. The tubes ordinarily should pass just far enough into the cavity to permit their retention. If there is difficulty in holding a tube in place a strip of adhesive through the pin and secured on the skin will usually suffice to hold it in place. Through one of the tubes one or two Carrel tubes are placed in such a way as to insure thorough irrigation of the cavity. The fenestrations in the tube, even if they do not project into the cavity, permit some degree of irrigation of the sinus tract, a feature which is very desirable. If instead of using free open drainage, as outlined here, it is desired to practice some one of the closed methods of suction drainage, it may be done. Here again, however, in spite of theoretical advantages, after an extensive trial of both methods, I am not at all convinced that practically any better results are obtained with methods of closed drainage. A device which we used in a considerable number of cases while on the Empyema Commission is shown in Fig. 32. Other measures which are sometimes resorted to for the purpose of excluding air are the use of valvular tubes of which many different kinds have been suggested. The simplest type consists of a tube the external end of which is covered with a loose piece of thin rubber or of some similar material which will allow fluid to escape from the cavity but which on inspiration will be sucked up against the opening in the tube and exclude air.

Not only have I not been convinced of any marked advantages of closed sucking devices for continuous drainage but there are even certain disadvantages. One of the principal objections is that with most forms of apparatus it is necessary for the patient to remain in bed. This is a distinct disadvantage because it is very desirable for all such patients to be up out of bed as soon as the heart and general conditions will permit. If, however, a valvular tube of some kind is used, or such a device as advocated by von Eberts,[82] or if a Politzer bag is put on the tube as recommended by Bryant,[83] then of course it will be possible for the patient to be out of bed. Mozingo[75] has claimed as one of the advantages of his method the fact that the patient can get out of bed early. There are other objections, also. One of these is the difficulty in keeping the tube and connections air-tight for more than a few days. In accordance with a general rule applicable to all foreign bodies in the presence of suppuration there is a tendency for the tube to become loosened. Müller[84] and others have also had the same difficulty. As soon as the tube becomes loosened a little, pus begins to collect around it; and if rubber dam or some similar material has been used to seal over the wound, the pus spreads around under it and excoriates the skin.

Early Sterilization and Obliteration of the Cavity.—The avoidance of an open pneumothorax during the pneumonic stage of an empyema will unquestionably result in a lower mortality. But a reduction in the mortality is not the only consideration in the treatment. Another principle of cardinal importance is the prevention of a chronic empyema. To accomplish this it is necessary both to sterilize and to obliterate the cavity. Unless both of these conditions are fulfilled permanent healing does not take place. There has been too much of a tendency among recent writers to consider as healed those cases in which the sinuses are closed and in which for the time being there is an absence of fever. It is impossible to be certain that an empyema has really healed until several months have elapsed without a recurrence.

Sterilization, when it really occurs, is actually accomplished by natural forces from within the body Antiseptics will not sterilize living tissues, especially those antiseptics which are applied to the surfaces of infected tissues. At best they will serve only to remove the infected necrotic tissue. Adequate drainage is by far the most effective artificial aid to natural sterilization which can be supplied. But in spite of apparently adequate drainage and in spite of irrigations with or without the use of antiseptics some cases of acute empyema become chronic.

The failure of these cavities to obliterate themselves in all probability has been due chiefly to an inability on the part of the lung of the affected side to expand sufficiently to fill up its side of the thorax. This inability to expand is dependent chiefly on two factors: (1) fibrosis of the lung as a result of inflammation and (2) the thick, inelastic coat of exudate which covers the exposed surface of the lung and limits its inflation. This thick coat of exudate may be likened to a

tightly fitting corset around the lung which obviously will interfere with its expansion, although actually of course it does not surround the lung.

Evidence of the failure of the lung to expand properly is presented at necropsies in cases of unhealed empyema. It is revealed by finding that the lung on the affected side is smaller than the opposite one, and that the exposed surface of lung is coated with a dense layer of exudate which is sometimes fibrinous and sometimes organized connective tissue, in association frequently with a lake of pus contained within the thorax. The inequality in the size of the two lungs has frequently been ascribed only to the collapse of the lung on the opened side from open pneumothorax, and it has even been used as an argument against the idea that the pressure effects of an open pneumothorax concern both lungs, as developed in the experimental part of this article. It seems more probable, however, that there are other explanations. In the first place, as MacCallum[42] has pointed out, "widespread necrosis occurs with final destruction of areas of lung substance." As this necrotic lung tissue is removed by expectoration and by gradual absorption, a considerable amount of fibrosis must occur during the healing process, which must necessarily result in the lung's being smaller than normal. At the same time the opposite lung may undergo hypertrophy, since the presence of long-standing adhesions and inflammatory induration have immobilized the mediastinum to such an extent that the healthy lung is no longer subjected to compression by slight changes of pressure in the affected pleural cavity. The remaining air-containing portions of the affected lung, however, are not able to undergo hypertrophy to the same extent as they might otherwise because of the thick coat of organized inelastic exudate which inhibits an adequate inflation of this lung.

It is obvious therefore that the early removal of this corset-like membrane is highly desirable. Because, at least in the streptococcal cases, organization of this exudate is known to occur early, it is clear that, other things being equal, the longer it is allowed to remain on the lung, the longer it will take to obliterate the cavity. For the cavity is obliterated only when the lung is in contact everywhere with the parietal pleura. In the past, recourse has been had chiefly to mechanical means for the accomplishment of this purpose, as, for example, decorticating operations of the general type as devised by Delorme;[85] but, although in some cases they have yielded brilliant results, on the whole they have been unsatisfactory. They have been associated with a high mortality and frequently they have not cured the patient. The fundamental defect in the rationale of such procedures is that attention is directed to only one of the two main objects of the treatment of empyema, namely, only to the obliteration of the cavity. It is fully realized of course that nature's efforts at sterilization are greatly aided by the obliteration of the cavity, but the frequency with which empyema recurs after the lung has apparently expanded to fill up the pleural cavity is evidence of the desirability of more active efforts directed towards the sterilization of the cavity.

In neutral 0.5 per cent. solution of sodium hypochlorite (Dakin's solution), on the other hand, we have an agent which, on theoretical grounds, should be nearly ideal as an aid to drainage. For not only will it help materially to sterilize the cavity but also, by its solvent action on the exudate, it will effect decortication and thereby help to obliterate the cavity. Clinical experience based on thousands of cases in army hospitals not only at our own hands but also at those of other observers have seemed to indicate very strongly that in the overwhelming majority of cases, if properly used, it will accomplish these purposes. Just recently, however, Wilensky[86] has questioned the superiority of Dakin's solution over simple irrigation.

For an extensive discussion of the details of its preparation and use the reader is referred to the book by Carrel and Dehelly[87] and to the report of the Empyema Commission.[65] We ordinarily begin the use of the Dakin's fluid immediately after the operation. The Carrel tube which projects outside of the dressings is attached to a bottle containing the solution and the proper amount is allowed to run in. Our custom is to give at first just a little less than the amount of exudate removed at operation. For example: If 250 c.c. of pus were removed, about 200 c.c. of the Dakin's fluid would be run into the cavity at intervals of about every two hours during the day, and of three or four hours during the night. The outside dressings can be changed as often as they become saturated. Once a day all the dressings are removed and the cavity is thoroughly flushed with the solution. Measurements of the capacity of the cavity are also made at the daily dressings, and as the cavity diminishes in size the amount of the Dakin's solution is likewise decreased. We believe that it is essential to use fresh solution which is not more than two days old and to protect the skin with vaselined gauze. If these precautions are carried out there will be few complaints of an irritation of the skin. Cultures should be made from time to time, preferably at intervals of three or four days, to note the progress in sterility. In a favorable case, after about three days there will be no more pus and in a week or 10 days no more bacteria will be found on culture.

The cavity may not be obliterated, however, by that time. Two procedures are then possible: (1) To close the drainage tract either by a simple plastic operation or by allowing it to close spontaneously after removal of the tube; or (2) to continue the irrigation and drainage until the cavity has obliterated itself, diminishing gradually the amount of solution used. The former method ignores the pneumothorax cavity in the belief that it will take care of itself without further trouble. This method gives quick brilliant results in the successful cases but I am convinced that it will also give more recurrences than the latter method. Stewart,[88] Mozingo,[75] Moschcowitz[40] and Heuer[89] have all advocated this procedure. It seems to me that the question is really one for the patient or his family to decide. If they would prefer to take the risk of a recurrence in order to save perhaps a couple of weeks of time the method would be justifiable. At present we are not in a

position to know very accurately what the risk is, since, so far as I am aware, there are no suitable statistics available showing the percentage of recovery. Certainly the cavity should not be considered as sterile until at least two or preferably three successive cultures showed no growth. No reliance should be placed merely on smears.

In a considerable proportion of cases (about 15 per cent. of the streptococcal cases) difficulty in irrigation is encountered because of the presence of a communication with the lung, a pleuro-pulmonary fistula, which permits the irrigating fluid to run into the lung. In such instances violent coughing will immediately follow the attempt to irrigate and, if Dakin's solution has been used, the patient will usually complain of the taste of chlorin. In the great majority of these cases spontaneous healing takes place in a few days. Our usual procedure in handling them is to stop all irrigation for three or four days and then try again. Usually on the second attempt no complaint of discomfort will be made. Sometimes by changing the position of the patient slightly it will be possible to irrigate even before the communication with the lung has healed.

The chief value of the Dakin's solution, it seems to me, is the fact that it sterilizes and obliterates the cavity chiefly through its power of dissolving necrotic tissue. Its direct antiseptic value is of minor importance, but it tends to prevent secondary infection. It is impossible to avoid the sucking of organisms into the wound no matter with what care the dressings are done; and in the past, patients with empyema have usually been infected with secondary organisms of all kinds so that the odor of a group of them in a single ward was often overpowering. The Dakin-Carrel technique certainly minimizes secondary infection, and army experience showed that it was possible to have fifty or more of these patients in a single ward without any disagreeable odor at all.

As a rule the decorticating effect exercised by the Dakin's solution is a gradual process which is accomplished by the gradual solution of the false membrane of fibrin and necrotic tissue. In some cases, however, this membrane is removed suddenly in one large mass or in several smaller pieces. As evidence of the decorticating ability of Dakin's solution an epitome of a striking case is here presented.

Private G., 22 years old, was wounded in the arm and leg in October, 1918, in the Argonne. He developed a pneumonia on the left side followed by empyema in November. He was drained through a thoracotomy incision. When first seen by me on June 2, 1919, at U. S. A. General Hospital 28 at Fort Sheridan, he had a small opening in the seventh interspace in the left posterior axillary line which was draining a considerable amount of pus containing large numbers of hemolytic streptococci. According to the patient's own account Dakin's solution had been used on him occasionally at some of the various hospitals in which he had been but never systematically. He was markedly underweight, had a septic appearance and had an afternoon temperature which ranged from 101 to 102°F. He had entirely recovered from the wounds of his extremities. A measurement of his empyemic cavity showed a capacity of 350 c.c. and the patient stated that a measurement which had been made two months previously had showed the same capacity. Under local anesthesia a portion of the seventh rib was resected, and

immediately after the operation instillations of 200 c.c. of Dakin's solution at two-hour intervals were begun with provisions for adequate free drainage. On the sixth day a large piece of tissue was found plugging the drainage opening. A photograph of this tissue after it had been hardened in formalin is reproduced here (Fig. 33). A description of it will be given later. Two days after the expulsion of this tissue the empyemic cavity would hold only 35 c.c. of fluid instead of 350 c.c. and no growth of bacteria was obtained from the secretion. Ten days later he was entirely healed and examination both by ordinary physical means and with the *x*-ray revealed no cavity remaining. On August 28 he returned from a month's furlough, apparently entirely well and having gained 35 pounds in weight. Two months later I heard from him again, and he was still entirely well.

FIG. 33.—Photograph of piece of tissue removed in a case of empyema as a result of irrigation which illustrates the decorticating action of Dakin's solution.

The rapid decortication with later sudden expansion of the lung to fill the cavity such as happened in this case is unusual, but I have observed it several times.

The piece of tissue was irregular in outline and flat. In longest diameter it measured nearly 6 cm. and in widest diameter about 3 cm. It was nearly 0.5 cm. in thickness. It was yellowish-white, smooth except for folds on its surface, and in gross appearance it closely resembled fibrin. In fact it was considered to be fibrin until microscopic sections were made. The microscopic examination, however, showed that the main portion consists of necrotic organized tissue. Except for a narrow strip of inflammatory tissue which evidently indicates the side attached to the lung the whole section is occupied by

bands of wavy fibrils, arranged parallel to one another, with here and there the faint remaining outlines of what apparently have been blood vessels. The entire absence of nuclei except in the inflammatory zone is striking. These fibrils are readily stained by Van Giesen's stain for connective tissue, but they are not stained by Weigert's method for fibrin. Undoubtedly, therefore, the tissue is chiefly fibrous connective tissue which has become necrotic and is not unorganized fibrin. Throughout the inflammatory zone, and occasionally in the area just beyond, are seen irregular clumps of organisms. Many of these can

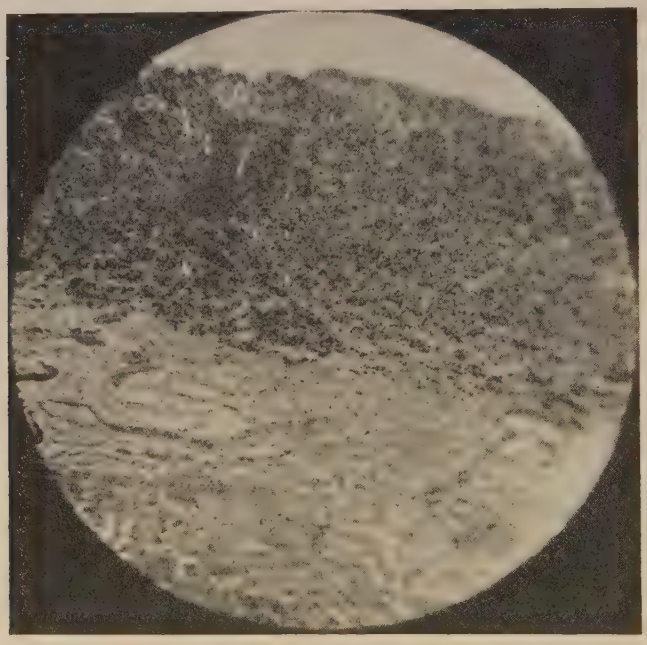


FIG. 34.—Microphotograph of tissue shown in Fig. 33.

be clearly distinguished as streptococci, and they are gram-positive. The accompanying illustrations (Figs. 34, and 35) show the principal features of this tissue which have been discussed here.

Despite the advantages of irrigation, which have been previously discussed, certain dangers are associated with it other than those due merely to a communication with the lung. Bleeding occurs sometimes. It is usually only slight in amount. I have never seen anything approaching an alarming hemorrhage result from irrigation, although cases have been reported in which large amounts of blood have been lost. Usually in cases of bleeding, if the irrigation is stopped for a day or two it may be resumed without further trouble. Attacks of syncope have been reported which in a few instances have been fatal. These have sometimes accompanied paracentesis or thoracotomy; and sometimes merely an irrigation has seemed to produce them.

Wilson Fox[89] in 1891 collected 17 cases of sudden death which he felt were due to some one of these procedures. Hippocrates is said to have observed the danger of fatal syncope in aspiration if the fluid were too suddenly removed. Some of these serious complications doubtless are due to cerebral embolism (Gee and Horder[91]); others are probably concerned with the pleural reflexes studied by Capps and Lewis.[71] In an experience with about 400 cases of empyema treated by irrigations under my own personal supervision I have never seen an attack of syncope in association with irrigations of the pleural cavity. On one occasion while witnessing a rib resection under local anesthesia for empyema the patient had two severe general convulsions while on the operating table, became comatose and died about thirty-six hours later. At necropsy a diffuse streptococcal meningitis was found. On another occasion a patient under the care of a colleague died suddenly with an acute dilatation of the heart about five minutes after being at stool. It is well to bear these dangers in mind, but they are of such rare occurrence that in my opinion they should not deter us from obtaining the advantages which irrigations present. In this connection a study made by Stevens[92] on recurrence in empyema is important. Of 56 cases with healing under simple drainage without irrigations, there were 14 recurrences, or 25 per cent.; of 67 cases healed under the Dakin-Carrel treatment with drainage, there were eight recurrences or only 12 per cent.

There are a number of other procedures of importance to hasten the expansion of the lung and promote healing. These consist in various exercises, both respiratory and general. Blowing against resistance is undoubtedly of value in hastening the expansion of the lung and thereby the obliteration of the cavity. For by this simple act air is forced from one bronchus into another in order to equalize the pressure in the two lungs. Children will often become inter-

FIG. 35.—High-power drawing of section shown in Fig. 34. The fibrils noted do not stain with Weigert's stain for fibrin, but do stain with Van Gieson's stain for fibrous connective tissue. They represent, therefore, necrotic fibrous tissue. This constitutes further evidence showing the decorticating action of Dakin's solution.

ested in blowing colored water from one bottle to another connected by a tube. Toy balloons to inflate, toy horns, etc., are also useful for this purpose with children. Properly graded general exercises are also of value, not only to increase the musculature and general condition of the patients but also to correct deformities (especially scoliosis) which are very likely to develop in children as a result of the empyema. It is essential, however, that the exercises should not be too violent at first, and it is wise to test the heart carefully before recklessly prescribing a

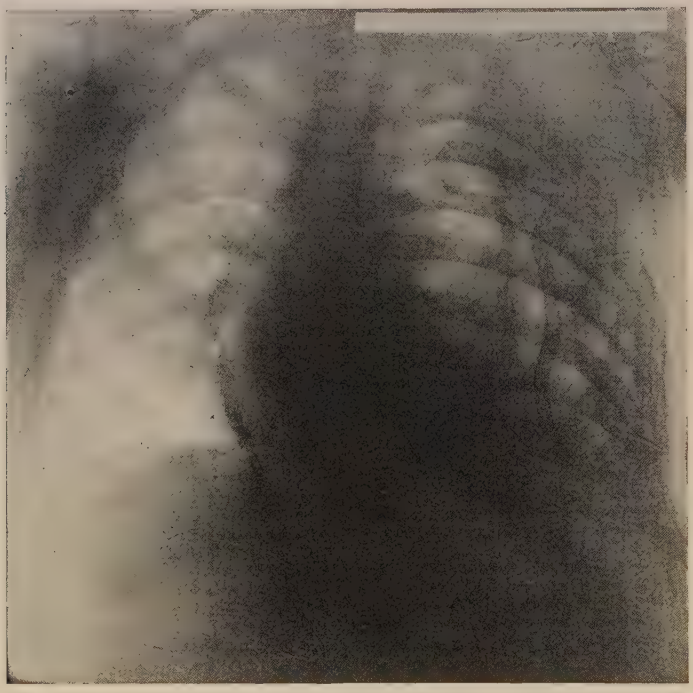


FIG. 36.—Skiagraph showing Carrel tube in place for irrigation with Dakin's solution in cases of empyema.

course of exercises, since a considerable degree of myocarditis is common.

Maintenance of the Nutrition of the Patient.—The third essential principle in the treatment of empyema is the maintenance of the nutrition of the patient. In this connection R. D. Bell[65] has made some very important observations during the army epidemic. Briefly, he found that unless special attention is paid to the nutrition of these patients they are likely to have a negative nitrogen balance amounting to a deficit (in adults) of as much as 21 gm. per day. A negative nitrogen balance was always found if the diet consisted of only 1500 or 1700 calories per day. If a patient is losing in his excretions 21 gm. of nitrogen per day more than he is taking into his body as food, it is

not surprising that he loses rapidly in weight. Obviously if this negative nitrogen balance continues very long, the disadvantageous effects of starvation are added to the handicaps under which he is already laboring in his efforts to combat a serious infection. If, however, the food intake is pushed so that he has a mixed diet contain-

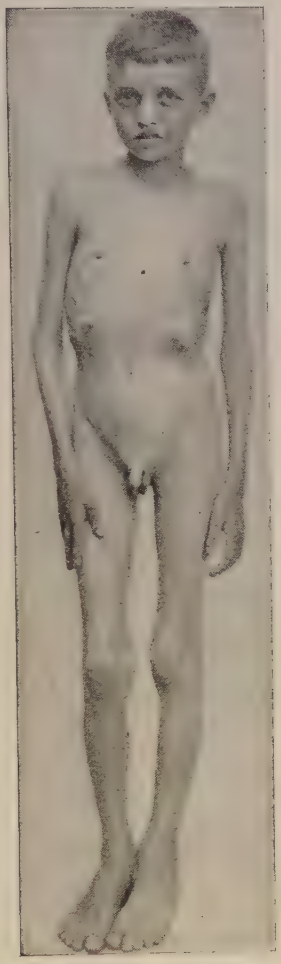


FIG. 37.—Emaciation in a child with neglected undrained empyema of the left thorax. Note also flattening of left side of thorax with bulging of right side. (From St. Louis Children's Hospital.)

FIG. 38.—Scoliosis in child shown in Fig. 37.

ing (in an adult) from 3300 to 3500 calories per day, his nitrogen balance will be positive and he will usually gain in weight instead of lose. It is very interesting in this connection that Bell found that the average daily loss of nitrogen in the pleural exudate in patients

who were aspirated amounted to only about 2 gm. as compared with from 20 to 30 gm. in the urine.

The advantages of preventing loss of weight and emaciation are so obvious that they scarcely need comment. Emphasis should, however, be placed on the fact that it is perhaps as important on the part of the surgeon to see that these patients are taking a sufficient quantity of food as to attend to any other part of the treatment of empyema. Undoubtedly many fatalities as well as the transition of some cases from an acute to a chronic stage are due to the neglect of this important

FIG. 39.—Same patient as shown in Fig. 37 three months after drainage.

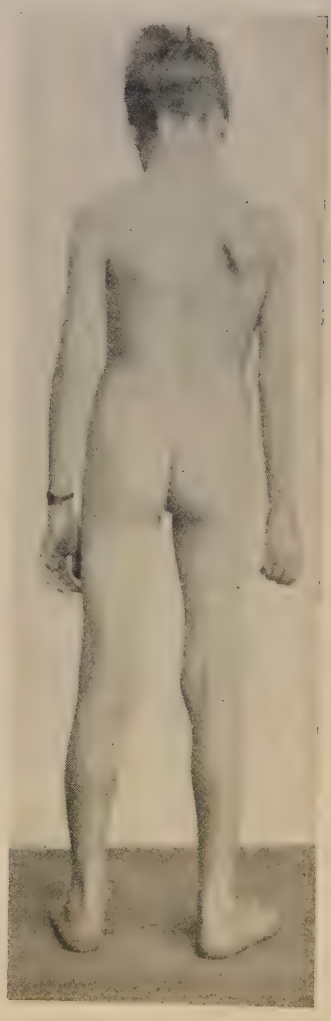


FIG. 40.—Posterior view of same patient showing scoliosis not yet entirely corrected although the case is completely healed.

feature. In the case of children with empyema it is always highly desirable for the surgeon to coöperate with the pediatrician in this respect. The patient should be weighed at regular intervals and the weights recorded. After drainage is instituted there is usually a considerable gain in weight. If the weight remains stationary or decreases, suspicion should be strongly aroused that either the empyema is not being drained adequately or that some other condition is present.

FIG. 41.—Skiagraph of same patient after healing. The scoliosis is still apparent and some thickening of the left pleura remains.

CHRONIC EMPYEMA

Chronic empyema in children is much less common than in adults. There is a tendency either for complete recovery or death. In two years' experience at the St. Louis Children's Hospital, I have seen only two cases of chronic empyema. This coincides relatively with the experience of others. In 150 cases of chronic empyema at the Mayo Clinic, Hedblom[93] found only 11 cases in children under 10 years of age.

The condition may be found either as a previously unrecognized accumulation of pus in the chest or as a case presenting a discharging sinus. It is remarkable that often a patient will go for a year or more with a very large accumulation of pus within the chest, frequently containing large numbers of hemolytic streptococci, without sufficient apparent local or general disturbance to make medical consultation seem necessary. The only symptoms complained of may be a cough, pain in the side, or loss of strength. On examination, however, in addition to the local evidence of fluid in the chest, there will also be found more or less emaciation, which may be extreme, fever of about 101 degrees in the afternoons, leukocytosis, and, especially in children, a scoliosis. An *x*-ray examination and an exploratory aspiration will furnish the additional evidence if necessary for the diagnosis.

Discharging sinuses are of several different types: (*a*) Those which merely lead into relatively large cavities; (*b*) those which communicate with the lung or with a bronchus but do not lead into a large cavity; (*c*) combinations of the above two; (*d*) sinuses which lead only down to the pleura or to a rib.

The most important causes of persistent sinuses are: (1) Inadequate drainage; (2) presence of foreign bodies; (3) communications with the lung; (4) cavities that cannot be obliterated spontaneously; (5) tuberculosis or similar infections. In an experience with 138 cases of chronic empyema at Fort Sheridan in the spring and summer of 1919, by far the most common cause was found to be insufficient drainage of the empyemic cavity. I am strongly of the opinion that one of the surest ways by which to turn an acute empyema into a chronic one is the failure to provide proper drainage. The various methods of closed drainage through small tubes and catheters have unquestionably saved lives during the acute peumonic stage, but in many instances they have also been responsible for the transition of an acute empyema, which should have healed, into a chronic unhealed one. It was appalling to find case after case in which treatment for 10 or 12 months had been supposedly by drainage, but in which the only provision for drainage was a tiny tube (often a Carrel tube) projecting from an opening no larger than itself, which would lead into a cavity containing 300 or 400 c.c. of pus, and even this tube would often be tied into a knot to prevent the admission of air! Moreover, so much faith had been placed in suction that in very many cases no attempt apparently had been made even to make the drainage opening at a dependent part of the cavity. These are the great dangers, it seems to me, in the unintelligent use of the various closed methods. The emphasis in the treatment of empyema has been placed too much on merely the reduction of the mortality during the acute stage and not enough on the prevention of chronicity. The treatment of empyema is still surgical, and its proper handling requires the judgment of an experienced surgeon. It cannot be turned over safely to an inexperienced person. Mozingo[75] states as one of the advantages of his method of treatment: "The post-operative treatment in greater part may be done

by a nurse or a properly instructed member of the family." What he means doubtless is that most of the irrigations can be done by someone with ordinary intelligence, but there exists among general practitioners too much of a feeling that a method like that of Mozingo's has made the treatment of the condition practically automatic.

Foreign bodies constitute another important cause of persistent sinuses. Of these, the principal kinds in civil practice are sequestra of ribs and pieces of various kinds of drainage material, notably tubes and gauze. Communications with the lung which may exist in association with persistent sinuses are of various kinds: (1) Pleuropulmonary fistula. This is the most common type. It is due probably to the rupture of a small subpleural pulmonary abscess into the pleural space. The communication with the lung may persist for a long time. Usually, however, it heals spontaneously. (2) Bronchial fistula; a communication exists with a large bronchus. This type is less likely to heal spontaneously, and the fistula frequently becomes lined with epithelium. It may be so large that the patient may be able to breathe comfortably through it. Both of these types may communicate only with the main cavity, or, as often happens in the case of a bronchial fistula, the fistula may communicate directly with the outside, and no other cavity may exist. Fistulæ which communicate with the lung frequently lead into abscesses or into areas of bronchiectasis. Some sinuses merely lead down to a rib or cartilage which is the site of a chronic infection without the presence of definitely demonstrable sequestra.

Cavities that cannot be obliterated spontaneously are in most instances due to improper management earlier in the course of the disease. They are usually found either in cases in which a free open drainage was instituted at too early a period or in cases in which adequate drainage has never been provided. In the work of the Empyema Commission we found that most of the largest cavities and those which gave the most difficulty in obliterating were in the cases in which an open drainage operation had been performed evidently in the pneumonic stage. At Fort Sheridan in 1919 I found that the cavities which were the most difficult to obliterate without a plastic operation were in patients in whom the disease had existed for a year or more with very inadequate drainage. The principal actual causes are that, due to the persistence of the infection, the exudate on the lung becomes organized into fibrous tissue which thereby limits its expansion, and the fact that the lung itself undergoes fibrosis and contraction. At the same time the increased rigidity of the mediastinum tends to prevent the crowding over of the other lung and mediastinal structures into the diseased side, so that the cavity persists.

It is well known that pleurisy due to tuberculosis and other similar types of infection (actinomycosis, etc.) does not heal readily. Sinuses in such cases tend to persist. Of the 138 cases of chronic empyema at Fort Sheridan, 13 (10 per cent.) were proved to be tuberculous. The incidence in children would probably not be so high.

Every patient with a chronic empyema should be examined carefully with reference to the nature of the infection, the size and contour of the cavity and the presence of foreign bodies.

Cultures should be made from the secretion obtained from well within the cavity and not merely from the sinus. Other methods, of course, should be used for determining the presence of a tuberculous or similar infection, such as the microscopic examination of a piece of the wall of the sinus, the examination of the sputum for the organisms, etc.

Many variations exist in the nature of the cavities found. Some are large, occupying practically the entire half of the thorax; others may have a capacity of only a few cubic centimeters. Some cavities are unilocular, but perhaps in the majority of cases of chronic empyema they are multilocular. The presence of adhesions causes constrictions in various places in what may have originally been a single large cavity, with the result that all sorts of irregularities in shape may occur. It is this irregularity in shape of the cavity that is very often responsible for the chronicity of the case, because proper drainage has been impossible under existing conditions. Especially is this the case in hour-glass constrictions.

It is very important, therefore, that as nearly as possible an exact diagnosis should be made of the size and contour of the cavity with which we have to deal. There are several methods available which are of great help. Instrumental exploration with a long flexible probe, such as a uterine sound, or with a pair of long curved dressing forceps will provide much information. The most valuable method of studying these cavities, however, is by means of the *x*-ray. The pneumothorax cavity will often reveal itself in a very satisfactory manner, especially if stereoscopic plates are made. Still more illuminating is the *x*-ray study after the injection of various opaque substances. For this purpose various substances have been used, chief of which are bismuth or barium pastes or emulsions and solutions of thorium nitrate or of iodids (sodium or potassium). The solutions, either of thorium or of the iodids, have advantages in that they readily fill up and distend a cavity regardless of its constrictions and tortuosities, and they can be easily removed. But, on the other hand, they cannot be used if there is a pulmonary or bronchial fistula; and in addition they frequently give rise to a considerable amount of irritation which sometimes results in rather severe bleeding. Bismuth paste is usually satisfactory, but it is safer to remove it immediately after the *x*-ray examination not only because of the danger of bismuth poisoning but also because it is likely to plug up the discharge. Stevens[94] has shownthat bismuth in olive oil may be injected and allowed to run out again immediately with the result that a thin film remains which gives a satisfactory outline of the cavity.

Tuffier[95] has used to his satisfaction a modified cystoscope which he inserts into the chest cavity and in that way gets a direct vision of the conditions present. It will often happen, however, that in order to

obtain the necessary impression of what the conditions actually are an operation will be required. Even sequestra from a rib will often fail to show in the *x*-ray plate because of the obscurity caused by a greatly thickened pleura.

Treatment.—The kind of treatment recommended will vary greatly according to the particular case. The main indications are to provide adequate drainage, remove foreign bodies, accomplish sterilization, and then to supplement with operative procedures, if necessary, to hasten the obliteration of the cavity. General hygienic measures are also very valuable.

It is well to begin the treatment of the ordinary case of chronic empyema rather conservatively; for it is often amazing to see how much can be accomplished merely by establishing adequate drainage and promoting sterilization of the cavity. The old sinus, therefore, should be enlarged to whatever degree may be necessary in order to secure a proper inspection and examination of the old tract and the cavity. This will almost always require the resection of a portion of one or more ribs. The ribs around the old sinus may be found fused together, or in regenerating they may have assumed various bizarre shapes. It is not uncommon for the sinus tract to be surrounded by a ring of newly formed bone. Having explored the old tract and the cavity for foreign bodies, the object then should be to secure satisfactory drainage. To accomplish this it may be necessary to convert a multilocular cavity into one which is unilocular. This may require the separation of adhesions at various points and perhaps a considerable amount of greatly thickened pleura can be removed safely at this time. If the opening already made is not in a position which will drain the dependent portion of the cavity, either it should be extended downwards or a new opening should be made. It cannot be too strongly emphasized that free drainage is the most important indication of all in the treatment of these cases. In the ordinary case I think this is all that should be done at first. My own preference is to put no sutures into the wound but to place several Carrel tubes in advantageous locations, leaving one or two drainage tubes of large caliber in the wound to prevent too rapid closure. There is no fear of serious danger from pneumothorax in this type of case because the presence of adhesions and inflammatory thickening have stabilized the mediastinum. Irrigations with Dakin's solution are begun at once.

It was a frequent observation in the work of the Empyema Commission that often very large cavities which had remained practically stationary for months would become rapidly obliterated as soon as sterilization was accomplished by combining satisfactory drainage and irrigations with Dakin's solution. Hedblom[93] has presented an interesting table which shows the reduction in size of the cavities in 51 cases of chronic empyema (all existing over three months) accomplished by a combination of free drainage and irrigations with the Dakin's solution.

Cases	Capacity of cavity in cubic centimeters	Average number of days of treatment	Capacity of cavity at end of treatment in cubic centimeters	Average per cent. decrease in capacity of cavity
11	Less than 100	35.9	10	90.0
16	100 to 250	34.1	11 to 27.5	89.0
15	250 to 500	56.4	11 to 22	95.6
5	500 to 1000	45.2	11 to 22	97.8
4	1000 to 2000	32.0	80 to 160	92.0

	Cases
Complete recovery	34
Sinus at last report	6
No late report	6
Convalescence not completed	4
No benefit (tuberculosis)	1
	51

The advantages of a plan of procedure such as outlined above are not only that in many cases healing can be obtained in this way with a minimum of risk and of deformity but also that, if a more severe plastic operation becomes necessary later, it can be done in a relatively clean field.

As already indicated, however, there are some cases in which healing cannot be secured by this comparatively simple procedure. For such cases a more elaborate operation will be required. Operations for this purpose, of which many have been devised, have been developed along two different ideas. One of these was that in order to obliterate the cavity the rigid chest wall should be made non-rigid in order to fall down upon the non-expanding lung, and the other was to free the lung from its inelastic coat of fibrin and fibrous tissue in order to permit it to expand to meet the chest wall. The former was illustrated particularly in the operations devised by Estlander[96] and by Schede.[97] Estlander's operation consisted in the multiple resection of ribs; and Schede added to this the resection of the thickened parietal pleura. For details, reference may be made to the original articles or to any textbook of operative surgery. The other type of operation was originally suggested by Fowler[98] and almost simultaneously by Delorme.[99] It carried out the idea now generally known as decortication, by which was meant the stripping off from the lung of the fibrous tissue which prevents its expansion.

There are many objections to operations of this type. In the first place they all carry with them a high mortality and a low percentage of complete cures, so that a patient has very little assurance of a complete relief from his trouble even if he undergoes the serious risk

entailed by the operation. This is well borne out in the following statistics of Tuffier:[99]

Operation	Mortality, per cent.	Cure, per cent.	Per cent. of cases requiring another operation
Estlander	18	50	32
			Per cent. of cases not followed
Schede	28	50	22
Delorme	15	48	37

Extensive decortication is usually accompanied by a considerable amount of hemorrhage, and in many cases it is impossible to accomplish because the fibrous tissue on the surface of the lung is only part of a more general fibrosis of the whole lung and projections of scar tissue extend from the surface deep into the substance of the lung.

The Estlander and Schede type of operations leave a very bad deformity which is not only anatomical but physiologic as well. Recently, I had under observation at the Barnes Hospital a young woman upon whom a Schede operation had been performed some years previously. At the time of my examination not only was there the usual marked visible deformity but a determination of her vital capacity showed a reading of only 50 per cent. of what the normal is for a woman of her size, according to the figures of Peabody and Wentworth. She had a permanent handicap, therefore, of 50 per cent. in her vital capacity which is a very serious matter, because it means that if she ever acquires a condition which in itself lowers the vital capacity, her chances of recovery will be considerably decreased as compared with an individual who at the start had a normal one. Such conditions are pneumonia or any other pulmonary disease, an uncompensated heart lesion, etc.

Various modifications of these thoracoplastic operations have been suggested, some of which will be mentioned briefly. Souligoux,[66] recognizing the difficulties of decortication, has advocated the separation of the adhesions at the periphery of the cavity. This mobilization of the lung allows those parts of it which are still capable of inflation to expand and even to hypertrophy so that the lung is sometimes enabled to expand sufficiently to fill a cavity which otherwise it could not do. He combines with this procedure a modified Schede operation. Ransohoff[101] advocated gridiron incisions in the pleura over the lung with the idea of allowing it to expand. Robinson[102] has practiced the transplantation of flaps of muscle, particularly the latissimus dorsi, in order to fill up a cavity with living tissue which will provide granulations. Tuffier and Depage[103] advocate closure of the pneumothorax cavity after cultures have shown streptococci to be

absent and after the pleura has been shown not to secrete when dressed only with sterile gauze without the further use of Dakin's solution. In other cases he performs various combinations of decortication and mobilization of the lung. Heuer[89] has also closed some chronic empyemic cavities after sterilization, disregarding the pneumothorax. Beck[104] has transplanted flaps of skin into the cavity. Lambotte[105] had enthusiastically advocated the same procedure in intractable empyemic cavities in 1911.

The treatment of fistulæ which communicate with the lung deserve mention. It has been stated elsewhere that the small pleuropulmonary fistulæ which occur commonly in acute empyema usually heal spontaneously. Sometimes, however, fistulæ of this sort persist. They then probably connect with a small bronchus. It is common to find small areas of bronchiectasis in the portion of lung into which some of these fistulæ lead. In such cases the fistulæ really act as safety-valves discharging purulent material from the diseased portion of lung. They commonly attain the size of 2 or 3 mm. in diameter or even larger and they are often very long and tortuous. The external opening may be at a distance of 6 in. or more from the connection with the lung. These pursue rather a typical clinical course. Spontaneous closure frequently occurs and continues for a few days, or perhaps a couple of weeks at a time, during which time the patient will have a sense of fulness in the side, will show some fever and will often cough up pus. The fistula then opens again spontaneously, pus drains out, and the patient is relieved of symptoms. There may be no empyemic cavity left in the ordinary sense, and the fistulous tract may be the only evidence that the original empyema has not healed. An experience with a considerable number of such cases has convinced me that they should be treated radically. The fistulous tract should be dissected up and a partial resection of the lung should be made, including the diseased area. It is not necessary to make an extensive resection and the edges of the lung can be sutured together again with catgut as in any other pulmonary resection which includes only a portion of a lobe. Less radical measures consist in excising the sinus down to the lung, cauterizing the pulmonary opening and suturing it across. In one case I buried the stump of the sinus and the lung and covered it over with healthy lung tissue in much the same way as an appendix stump is buried in the cecum. The true bronchial fistula usually communicates with one of the main bronchi or with one of its principal branches. It may sometimes be almost large enough to insert a finger into it; and not infrequently it is possible for a patient to breathe through it comfortably with his nose and mouth occluded. Recent bronchial fistulæ, even of large size, may close spontaneously. In a patient upon whom I performed a lobectomy a bronchial fistula was present for six weeks which was large enough to permit respiration through it. Three weeks later it was entirely closed, and it stayed healed. Those which persist for several months, however, are usually permanent and require operative correction. The most satisfactory results are

obtained when the fistula is dissected up to its communication, cut off, and the opening closed after cauterization of the epithelium. Eggers[106] has written an article dealing exclusively with this subject which gives some good points in the treatment of the condition.

Another method of limited value in the treatment of chronic empyema and of chronic sinuses in the chest is the use of Beck's[107] bismuth paste. My own experience with this method has been limited but very unsatisfactory. When fistulæ are present the paste is very likely to be disseminated through the affected lung and even into the other lung. If sequestra or other foreign bodies are present the paste will serve only to prevent drainage by plugging the opening. There is also always the danger of bismuth poisoning.

As in the treatment of acute empyema, it is important to give a generous mixed diet. The rapid gain in weight which occurs in these cases after establishing satisfactory drainage is often astounding; in the case of adults it is common to have a gain of as much as 30 or 40 lb. in the first month. It is advisable also to keep these patients out in the open air continuously if possible. Blowing exercises are also helpful as in acute empyema.

TUBERCULOUS PLEURISY

Tuberculosis of the pleura is comparatively uncommon in children. It becomes of importance surgically only when it is secondarily infected with pyogenic organisms and pus is present. A true empyema must be treated along the lines already extensively discussed concerning empyema. The prospect of complete healing is bad. It is possible, however, that good results might be obtained by frequent aspirations combined with an extrapleural resection of ribs, similar to the method advocated by Friedrich for the treatment of pulmonary tuberculosis.

TUMORS OF THE PLEURA

Tumors of the pleura are exceedingly rare in children. They will therefore not be discussed in detail. Benign tumors of considerable interest are sometimes present. Tumors of aberrant lung tissue have been observed, as for example by Muus.[108] Cysts of the pleura which contained cartilage and ciliated epithelium, suggesting their origin in the bronchi, have been reported by Stilling[109] and by Zahn.[110] Lipomata which arise in the subpleural fat sometimes project into the pleural cavity. Fitz[111] reviewed the literature on the subject and reported a case. Occasionally lipomata of the thoracic wall which appear superficially may also extend into the pleura. Krönlein[112] reported a case in a female infant one year of age in whom he found that a lipoma which was situated in the anterior chest wall had a narrow pedicle passing through the third interspace close to the sternum and connecting with a large lipoma which almost filled the anterolateral portion of the thoracic cavity.

Of the primary malignant tumors the most common in general is the endothelioma. This tumor, however, is so rare as to be almost

unknown in childhood. One case has been reported by Hibler[113] in a child of five years. Reported cases were collected from the literature and published in 1905 by Bloch.[114] Doubtless it is frequently overlooked by being mistaken merely for thickened pleura as a result of a pleuritis. There is an excellent description of the pathology in Ewing's[115] book. Beginning as a group of nodules or elevations the tumor gradually converts the pleura into a diffuse, firm opaque mass covering and compressing the entire lung. A serofibrinous or bloody exudate usually accompanies the growth. Metastases occur.

Sarcoma as a primary tumor of the pleura is also extremely rare but a few cases have been reported in childhood by Bernard.[116] A spindle- and round-cell sarcoma weighing 1250 gm. was successfully removed from the pleura by Garrè.[117] Secondary sarcoma of the pleura may occur with sarcoma of any part of the body. It needs no special comment.

ECHINOCOCCUS DISEASE OF THE PLEURA

Primary echinococcus disease of the pleura is rare. Usually the process begins in a neighboring organ and finds its way into the pleura. The cysts may become secondarily infected and resemble an encysted empyema. The symptoms are chiefly those of an intrathoracic tumor. Surgical removal is the only successful treatment. The rarity of the condition in this country makes further discussion of it unnecessary.

SURGICAL DISEASES OF THE LUNGS

Abscess and Gangrene

These two conditions will be considered together because they merge into each other and are indistinguishable both pathologically and clinically. The tendency to consider them as separate entities and the attempts to make an arbitrary line between them seem to me to be unwise because no advantage is to be gained from it.

Incidence and Etiology.—Pulmonary abscess may occur at any age. Orth[118] and Silbermann[119] have each called attention to the abscesses present even in the newborn. The latter found that out of 12 cases the mother was septic in 10, a finding which lends support to the idea that these are essentially aspiration abscesses. Hartwell[120] states that in 6000 necropsies at the Bellevue Hospital, New York, there were 148 cases with the anatomical diagnosis of lung abscess and gangrene. Of these 148 cases he thinks there were only 50 in which the abscess was of sufficient size to be recognized by clinical means.

Important etiologic factors are: Pneumonia, of either the lobar or lobular type, foreign bodies in the bronchi or lungs, bronchial stenosis (either caused by pressure from without or from within), septic emboli, trauma, perforation of the esophagus, etc.

Pneumonia of some variety is by far the most important etiologic factor. In Tuffier's[121] list of 49 cases submitted to operation, 23 were postpneumonic. The incidence of abscess in lobar pneumonia is rare, however. Aufrecht[122] found only three abscesses in 253 fatal cases of lobar pneumonia, a finding which closely agrees with Fränkel's[123]

observation of about 2 per cent. in 1200 cases of lobar pneumonia Lord states that of 50 cases of pulmonary abscess at the Massachusetts General Hospital 14 could be traced to lobar pneumonia. Hartwell[120] states that in 770 consecutive cases of pneumococcal lobar pneumonia admitted to the Rockefeller Hospital, New York, only two developed lung abscess, and each of these showed other infecting organisms. Hartwell considers that the pneumococcus is not an important factor in the production of lung abscess, that the staphylococcus aureus is often responsible and that the condition frequently is a primary lesion in that a true pneumonic consolidation as connoted by the name pneumonia does not precede it. Opie, Blake, Small and Rivers[124] in a study of the influenzal pneumonia likewise found that the pneumococcus was relatively unimportant in the production of abscess but that hemolytic streptococci and staphylococci were evidently responsible for most cases of abscess occurring in this type of pneumonia. The following table summarizes their findings in this respect:

	Pneumococci			Hemolytic streptococci		Staphylococci		B. Influenzæ	
	Number of cultures	Number positive	Per cent. positive	Number positive	Per cent. positive	Number positive	Per cent. positive	Number positive	Per cent. positive
Bronchus	24	5	20.8	22	91.6	12	50.0	18	75.0
Lung	36	9	25.0	30	83.3	14	35.6	8	22.2
Blood	37	6	16.2	31	83.8				

Abscess is more common after influenzal and bronchopneumonia than after lobar pneumonia. But it is particularly likely to occur in those cases of pneumonia which are due to the presence of a foreign body. The cases following tonsillectomy are essentially of this sort, most of them probably being due to the aspiration of blood and infected material. Hedblom[125] has called attention to the importance of foreign bodies of dental origin. He has collected 52 cases of this nature.

Hartwell[120] found the essential etiologic factor in his series of cases to be the following:

Bronchopneumonia	29
Lobar pneumonia	18
Pyemia	15
Septicemia	11
Thrombosis in peripheral venous channels (sinus, jugular and inferior vena cava)	8
Septic endometritis	7
Infective endocarditis	6
Acute suppurative otitis media	5
Thrombosis pulmonary artery	4
Purulent bronchitis (cause or effect)	3
Tracheotomy	2

W. S. Lemon[126] in a study of 81 consecutive cases of lung abscess at the Mayo Clinic found etiologic factors as given below:

Pneumonia	31
Colds, grippe, pleurisy, asthma, typhoid, measles and scarlet fever	19
Operations:	
Teeth extraction (elsewhere under general anesthesia)	7
Tonsillectomy (elsewhere under general anesthesia)	5
Appendectomy	2
Gastroenterostomy	1
On gall-bladder	1
Excision of gastric ulcer	1
Trauma	2
Unknown	12

The importance of tonsillectomy as an etiologic factor is strikingly emphasized in a recent article by Wessler[127] who in a study of 100 cases of lung abscess found that 21 had followed tonsillectomy. General anesthesia seems to be an important contributory factor in these cases, probably because aspiration more readily occurs than if the patient is not unconscious.

Pathology.—Abscesses are more common in the lower lobes than elsewhere. In Tuffier's[121] series, 80 per cent. were in the lower lobes. In 292 cases studied by Lemon,[126] the lower lobes were involved in 192, the upper in 86 and the middle in 14. Hartwell's[120] figures in 50 cases, however, are different; 25 were in the upper lobes, 22 in the lower lobes and 3 in the middle lobe.

Lung abscess may be single or multiple. It is only the former type, as a rule, which is amenable to surgical treatment. Sometimes there is no well-defined abscess but instead a considerable area of disintegrated lung tissue infiltrated with pus and presenting an appearance somewhat like that of a sponge. In such instances the periphery of the abscess may be merely hepatized lung tissue. Usually the abscess is nearer the periphery than the hilus. The result of this is the production of adhesions between the lung and the chest wall in many cases. Points of special interest in the pathology were noted by Hartwell[120] as follows in his series:

	Cases
Subpleural abscesses associated with empyema	34
Abscesses ruptured into pleura accompanying empyema	12
Empyema draining through the trachea	2
Abscess ruptured into bronchus	15
Pus with markedly foul odor	47
Abscess result of necrosis of infarcted area	17

Gangrene of the lung occurs when a necrotic portion is invaded by putrefactive organisms. The accessibility of all parts of the lung to such organisms allows the production of some degree of gangrene frequently when necrotic tissue is present. Guillemot[128] and Veillon

and Zuber[129] have particularly called attention to the importance of anaerobic bacteria in the process. Laënnec[130] who first described gangrene of the lung recognized two main types, a circumscribed and a diffuse. In the latter a whole lobe or even a whole lung may be involved. This type is less common than the circumscribed. Laënnec distinguished three stages in the process: (*a*) Gangrenous eschar, the affected area being moist but firmer than normal and black or green in color, (*b*) liquefaction and (*c*) excavation. In Heusel's[131] series of 83 cases studied at autopsy, 17 per cent. were ascribed to pneumonia and 13 per cent. to pulmonary tuberculosis. Macewen[132] reported a case in which the whole left lung was one large abscess cavity; on incision, 160 oz. of pus containing tubercle bacilli and pyogenic organisms were evacuated. As is always the case in pulmonary suppuration abscess of the brain occurs as a not infrequent complication. Clubbing of the fingers and toes may also be marked.

Symptoms and Diagnosis.—Abscess of the lung is sometimes easily diagnosed but at other times it is impossible. Obviously it is only the large abscesses which can be recognized clinically. The most important means of diagnosis is the *x*-ray. In some cases a diagnosis can be made with certainty by the *x*-ray alone, although of course it is important that clinical signs should be present to confirm it. An abnormal shadow is seen within the substance of the lung which is not so sharply defined as in tumor or not even so well defined as in an interlobar or an encysted empyema; a gradual haziness extends out in all directions from the central portion. It may resemble an area of pneumonia, unless a cavity with fluid is present. In the latter case the sharply defined level of the fluid is seen with air above it; and often by changing the position of the patient the level of the fluid will be seen to change. This finding is pathognomonic of an abscess cavity with gangrene which has progressed to a stage of excavation. In cases with an associated empyema the diagnosis is more difficult because of the obscurity produced by the fluid. Stereoscopic plates are of very great value in accurately localizing the abscess. An additional advantage offered by the *x*-ray is the recognition of foreign bodies.

The symptoms are often extremely indefinite. In the pneumonic cases suspicion may be attracted to the possibility of abscess if the fever recrudesces or persists for a longer time than would be expected in an uncomplicated case, or particularly if the patient develops febrile symptoms after the crisis of a lobar pneumonia. Most commonly, however, such symptoms suggest an empyema. In cases which do not arise from a pneumonia, symptoms such as cough, fever, pain in the chest are often the earliest and most striking. Frequently the first sign which strongly indicates an abscess is the sudden expectoration of a considerable amount of pus which is coughed up because the abscess has ruptured into a bronchus. The sputum in such cases frequently contains elastic fibers, a finding of considerable importance. Purulent sputum often occurs in cases of suppurative bronchitis and sometimes also in cases of empyema which have established a communi-

cation with a bronchus, although no abscess, in the clinical sense, is present. The sputum usually is abundant and purulent. The odor may be very foul if any considerable amount of gangrene is present. Blood in the sputum is not uncommon and severe hemorrhages may occur in cases of extensive gangrene. Rilliet and Barthez[133] state that fatal hemorrhage has occurred in one-fourth of the cases of pulmonary gangrene.

On physical examination of the chest, the abscess may present its evidence if situated near the periphery of the lung but not necessarily if it lies deeply within the substance of the lung. It is comparatively rare that evidence of a cavity is obtained by ordinary physical examination. The temperature is subject to considerable variation. In some cases it is high, but in others there is comparatively little fever. The leukocytes are almost invariably increased.

Marked prostration and delirium are common in the acute cases with extensive gangrene. In the gangrene associated with severe diabetes the constitutional effects may be extreme. In mild diabetes, however, a lung abscess may often give few symptoms and be discovered only accidentally. On the basis of physical examination the diagnosis may be particularly difficult in children because in them it is frequently latent, and also because of the absence of sputum.

The aspirating syringe should not be used in cases of suspected lung abscess unless one is certain that adhesions are present, in order to avoid the creation of an empyema. The only way by which one can be certain of enough adhesions to prevent leakage is by inspection at operation. It is safer to subject a patient to an exploratory operation under local anesthesia than it is to use a needle indiscriminately.

Treatment.—In recent years there has been an increasing tendency to treat many cases of lung abscess conservatively. Of the conservative methods of treatment, the most commonly used and the most effective are postural drainage and artificial pneumothorax. It is difficult at the present time to define with any degree of accuracy what the indications for surgical treatment should be. In general, however, it may be stated that those cases which grow worse or show no improvement after a reasonable trial of conservative treatment should be drained surgically. It is probable also that all of the very large abscesses which show a definite fluid level with the *x*-ray should be drained. It is impossible to know accurately the comparative mortality with and without operation. Verneuil[134] states that without operation the mortality is 80 per cent. Lenhartz[135] referred to statistics from three large Berlin hospitals in which the mortality in cases of gangrene without operation ranged from 57 to 70 per cent. Baron[136] collected seven cases of lung abscess in infants, which were treated non-surgically, all of whom died. One case which he added to the series, in which a drainage operation was performed, recovered. Garrè's collected statistics of cases treated surgically are as follows:

	Number of cases	Cured	Died	Mortality, per cent.
Abscess	182	148	34	18.5
Gangrene	281	197	84	29.3

Körte[137] performed pneumotomy on 28 patients for lung abcess or gangrene; 20 recovered and 8 died (28.5 per cent. mortality). Lord quotes statistics from the Massachusetts General Hospital which illustrate the striking advantage of early operation. In six cases of abscess or gangrene (three abscess, one gangrene and two either abscess or gangrene) with operation within three weeks to two months of onset five patients showed immediate improvement and were later discharged relieved; three were in perfect health after four to twelve years; two could not be traced; one died soon after operation and multiple abscesses were found at necropsy. In five cases of abscess or gangrene (three abscesses and two either abscess or gangrene), with symptoms existing for from nine months to four years, three patients died soon after operation, one failed to be relieved after several operations, and the last patient recovered.

The chief indication in the treatment is to provide for free drainage. In cases which are complicated by the presence of a foreign body it is obvious that that also should be removed. Chevalier Jackson[138] in his remarkable experience with 789 cases of foreign body in the air and food passages has repeatedly observed recovery in apparently undoubted lung abscess after the removal of a foreign body from a bronchus by means of the bronchoscope.

The first deliberately executed incision into the lung to drain an abscess is said by van Stockum[139] to have been made by Krimer in 1830. In recent years this procedure has been the most commonly practiced method in the treatment of both abscess and gangrene. The operation is performed in either one or two stages. An important consideration in the operative treatment is the prevention of an empyema. In order to guard against this possibility it is necessary to have a protective barrier of adhesions through which to conduct the drainage. Tuffier found that in his series, 87 per cent. had adhesions between the lung and chest wall but they were not always sufficiently firm or extensive to prevent leakage.

The safest method of procedure, therefore, seems to be somewhat as follows: After having localized the abscess by means of the *x*-ray a subperiosteal resection of about 2 in. of one or two ribs is made in that part of the thoracic wall which will be closest to the abscess. Local anesthesia is to be preferred. Then by inspection and palpation it is usually possible to tell whether the lung is adherent. If the evidence is certain that the adhesions are extensive and firm enough to prevent

leakage, an aspirating syringe may be used to locate the abscess precisely. When pus is found the actual cautery or a knife may be inserted into the cavity along the needle which has been left in as a guide. If there is any doubt, however, about the adhesions it is a much safer plan to create adhesions and to delay opening the lung for about a week. A very satisfactory method of carrying this out is suturing the lung to the parietal pleura and intercostal muscles. Several sutures are passed through both the chest wall and lung tissue in such a way that they form a circle about 3 or 4 cm. (1½ to 2 in.) in diameter. A continuous suture with a round needle should be employed. A commonly employed stitch for this purpose consists in inserting the needle each time between the points of entrance and exit of the last stitch. This adds an extra safeguard against leakage. Bevan[140] has suggested packing gauze soaked in iodin or iodoform against the unopened pleura to create adhesions instead of taking the suture described above. The opening into the lung itself, whether made by cautery or knife, is a painless procedure and requires no anesthesia of any kind. A good sized drain should be used but one whose walls are not too rigid. Either a cigarette drain or a soft rubber tube may be employed for this purpose. Irrigation should not be used. Gentle exploration of the cavity with the finger will sometimes reveal an unexpected foreign body which was not shown in the *x*-ray, but great care should be exercised not to break strands of tissues which are felt crossing the cavity. These often are blood vessels and very serious hemorrhage has resulted from the tearing of such bands. If severe hemorrhage occurs, it should be controlled by packing. In the average case healing occurs in from six weeks to two months.

In 1900 the removal of an entire lobe of the lung for abscess and gangrene was undertaken successfully both by Gluck[141] and by Krause.[142] Both patients were alive and well 9 and 11 years respectively after the operation. This is a procedure which has been performed a considerable number of times since then, for example by Perthes,[143] Garrè,[144] Lenhartz,[145] Lilienthal[146] and others. It is unnecessarily radical for the treatment of acute abscesses but in the chronic cases, particularly those associated with bronchiectasis, it is of much value and in fact is the only hope of complete relief in many cases. This will be discussed more fully in the section dealing with bronchiectasis. As Sauerbruch has suggested, the operation is likely to be disastrous unless the hilus is fixed by thickening or adhesions, because otherwise the stump of the bronchus becomes retracted into the mediastinum and gives rise to an acute suppurative mediastinitis.

Other methods of treatment have been used which are based on the principle of compression of the lung. These have consisted in the main in thoracoplastic operations with extensive rib resections and also in the creation of an artificial pneumothorax. Forlanini[147] reported a case in 1910 in which an abscess had been present for six years. It was said to have been healed for three years with treatment

only by artificial pneumothorax. Goldberg and Biesenthal[148] have collected 16 cases, including three of their own, in which the only treatment was by artificial pneumothorax. Of this number 75 per cent. of the patients were improved and 12 per cent. died. Tobiesen,[149] De Verlizier and Loiseleur[150] and also Rist[151] have reported successful cases. In the chronic cases, adhesions are present; and, as Green[152] points out, they are present at the particular place where theoretically collapse is desired. In certain cases the procedure may give good results, but at least at present the reported cases are too few to warrant drawing conclusions from them. Also, as is the case with most new therapeutic methods, there is a tendency to report the successes rather than the failures. In two of the cases studied by Wessler an artificial pneumothorax was performed and both patients died suddenly after the last insufflation. The *x*-ray showed a marked extension of the disease.

Still another method of treatment suggested by Sauerbruch and Bruns[153] is the ligation of the pulmonary vessels to cause shrinking of the lung. This does not seem to be a rational procedure; and so far as I know it has not been tried in abscess, although Sauerbruch has performed the operation twice in cases of bronchiectasis with some improvement.

Bronchiectasis

The etiology, pathology and diagnosis of this condition have been discussed elsewhere. Only the surgical treatment will be taken up here.

The surgical treatment of bronchiectasis is heartily condemned in most textbooks and articles which deal with this subject. It is not surprising that it should be; for the early surgical treatment was most irrational and ill-advised. Based on a mistaken idea of the pathology of the condition, simple incision was practiced with the idea of draining a cavity. Obviously such a procedure was doomed to failure for the simple reason that little, if anything, could be accomplished by the drainage of only one of many purulent cavities or dilated bronchi in the lung. Difficulty in diagnosis gave rise to much confusion between abscess and bronchiectasis, and operations were sometimes undertaken with the erroneous idea that the patient was suffering from an abscess which could be relieved by simple incision. Moreover, as a rule, the operation was undertaken as a last resort in patients who were exceedingly poor surgical risks.

From a statistical point of view the tale is exceedingly mournful. Quincke[154] reported 15 cases in which the patients were treated almost entirely by incision into the lung. Of these one was entirely healed, six (40 per cent.) were improved, two (13 per cent.) remained unhealed and six (40 per cent.) died as a direct result of the operation. Thus 53 per cent. were either unhealed or died. Tuffier's[155] statistics are:

Operation	Cases	Improved or healed	Died	Mortality, per cent.
Pneumotomy	38	28	10	26.3
Pneumonectomy	1	0	1	100.0
Thoracoplasty	1	0	1	100.0
Puncture (trocar)	5	3	2	40.0

Körte[156] in a series of 21 cases had the following results:

Operation	Cases	Healed	Died
Pneumotomy	15	4	11 (73.3 per cent.)
Unfinished operation	2	1(?)	1
Putrid empyema after bronchiectasis	4	0	4

Garrè[157] in 1901 reported on 36 "healed" cases out of 57; but he considered that of these 36 cases, surely not half were really healed. Sauerbruch in collecting these various cases finds that of 123 cases of bronchiectasis which were treated by pneumotomy, 40 (33 per cent.) were said to have been healed, 7 (6 per cent.) were improved, 33 (27 per cent.) were unhealed, and 43 (35 per cent.) died. It is doubtful, however, if as many as 40 cases of true bronchiectasis have been actually healed by simple incision. The confusion in diagnosis between bronchiectasis and lung abscess which prevailed at the time when many of these cases were reported makes it more probable that many of the alleged successful cases were of lung abscess instead of bronchiectasis.

Sauerbruch has operated in two cases by his method of ligating the branches of the pulmonary artery to the lung. Both cases were said to have shown improvement as to the amount of sputum, but certainly, as described in his report, the results could not be considered as at all satisfactory. The object of the operation is to cause shrinking of the lung with the idea of compressing the bronchial dilatations. Based on a similar idea is the treatment with artificial pneumothorax in an attempt to collapse the lung. Thoracoplastic operations have also been performed with the same idea. All of these collapsing methods will frequently make a patient feel a little better temporarily and will diminish the amount of sputum, but the fundamental defect in this type of procedure is that it will not arrest the progress of the disease; as a rule, the relief gained is only temporary. Such methods really treat a symptom rather than the disease itself.

There is only one rational method theoretically, and that is the removal of the diseased portion of lung. From the nature of the

pathology of the condition, no matter whether it is cylindrical, sacculated or fusiform, it is hardly to be expected that healing of the dilatations could occur. Removal of them, therefore, seems necessary. To Heidenhain[158] apparently belongs the credit for first undertaking deliberately the removal of a lobe of the lung for bronchiectasis. He removed the left lower lobe after two previous operations had been done for drainage. In 1914 Meyer[159] found that 16 cases had been reported in which pneumectomy had been performed for bronchiectasis. Of this number eight were classed as cured or improved and eight died. He[160] reported in 1915 another case operated on successfully by himself. Lilienthal[161] in 1916 reported seven cases of his own*

FIG. 42.—Photograph of left lower lobe of lung successfully removed by author for bronchiectasis in a boy 17 years old.

of which four patients were said to have been cured and three died. Robinson[162] in 1917 reported five cases in which he had made a complete removal of a lower lobe with one death. Recently (December, 1920) in a case not yet reported I successfully removed the left lower lobe for bronchiectasis in a boy 17 years of age who had had symptoms of the disease since the age of three. When last seen (August, 1921) he

* In an article by Lilienthal which appeared since this manuscript was prepared he reports 24 cases of chronic pulmonary suppuration in which he removed one or more lobes ("Resection of the lung for Suppurative Infections, with a Report Based on Thirty-one Operative Cases in which Resection was Done or Intended," Ann. Surg., lxxv (1922) p. 257.) There was a total mortality of 54 per cent. In twenty-one cases the resection was performed because of the diagnosis of bronchiectasis. Of this number, seven patients (33 per cent.) were reported as well; twelve (57 per cent.) died, and, of the remaining two patients, one was reported as convalescent and the other as still having cough and expectoration, although his wound was healed.

had been entirely healed for four months with no evidence whatever of a bronchial fistula, and he was entirely free from symptoms (Figs. 42, 43).

In 30 known cases, therefore, of pneumectomy for bronchiectasis 12 have died, an operative mortality of 40 per cent. Moreover, of the 18 who have survived the operation, not all have been completely relieved of symptoms and some have been left with troublesome bronchial fistulæ. Smith and Mudd[163] in 1917 carefully analyzed the cases reported up to that time, and they believe that only three are complete successes, two of Lilienthal's cases and one of Robinson's. I would venture to add the case of my own, the full details of which will

FIG. 43.—Patient eight months after lobectomy for bronchiectasis. The healing has been complete for five months. There is no disability. The patient has gained 25 pounds in weight and is completely relieved of his former symptoms.

be published soon. This then, out of the 30 cases, would make four cases (13 per cent.) in which the result has been entirely satisfactory.

One is tempted to conclude from the foregoing analysis that any operative procedure which carries with it a 40 per cent. operative mortality and only a 13 per cent. chance of complete success should be abandoned. On the other hand, there are many reasons why such a conclusion should not necessarily be drawn. In the first place, in many of these cases lobectomy has been done only as a last resort on patients who were extremely bad risks for any important surgical procedure. If a better selection of cases had been made, doubtless the results would appear much better. A complete relief from all symp-

toms cannot be expected from the removal of one lobe if other lobes are involved. Furthermore, when advanced changes have occurred in other organs as a result of many years of suppuration in the lung, good results are hardly to be anticipated. Yet in general, it has been this very type of case which has constituted most of those in which lobectomy has been performed. Unquestionably better results would be obtained if the operation were limited to young patients in whom the process is confined to one lobe and has not run a sufficiently prolonged course to affect seriously the kidneys, heart and other viscera. Thoracic surgery is still in a very undeveloped condition; and improved methods together with a better knowledge of the fundamental physiology involved in operations within the chest will almost certainly improve results. In all important operations the mortality at first has been high. For example, as recently as 1905, Matti[164] compiled statistics from German clinics on the operative mortality in carcinoma of the stomach and found rates varying from 68 to 17 per cent. (average 43 per cent.). Yet by 1909 at the Mayo Clinic the operative mortality (partial gastrectomy and pylorectomy) had been reduced to 8.6 per cent.[165]

Bronchiectasis, of course, in general, affords a longer prospect of life than does cancer. But yet like cancer it is a progressive disease, and the danger of a sudden termination of life by some such complication as hemorrhage, brain abscess, etc., is very real. Lobectomy in properly selected cases offers a better chance of complete recovery than does any operation in cancer of the stomach; and even if the operation is not completely successful the patient who survives is almost assured of great improvement in his condition, which has been so graphically described by Robinson[162] in these words:

"Bronchiectasis is a chronic, loathsome disease, generally regarded as incurable. The expectoration is disgustingly profuse; consequently the afflicted loses employment, shuns society, becomes a recluse, and not infrequently resorts to dissipation. He is pale and a trifle cyanotic. His fingers and toes are clubbed. He labors with early fatigue. He coughs spasmodically, with varying persistency. Stooping, laughing, eating, hurrying, flood his trachea with pus and he retires, embarrassed, to drain himself of abundant sputum. In winter he is periodically ill with severe "colds," sometimes with bronchopneumonia, nor does the mildness of summer rid him of chronic cough. He may live many years, till cerebral abscess, pneumonia, septicemia, amyloid disease, or hemorrhage happily ends his existence."

The principal dangers in the operation of lobectomy are: (1) Those dangers with which a serious operation are always associated in a subject whose general condition is poor, and (2) the danger of infection, particularly of the mediastinal space. These patients are always the victims of a more or less chronic sepsis, they are underweight, anemic and usually somewhat cyanotic. In addition they have some impairment of kidney function. The danger of infection of the mediastinal space is very great. The stump of the bronchus always contains

bacteria, and it is of course in direct communication with the mouth and upper air-passages. If the mediastinum is not stabilized by induration and by adhesions the bronchial stump is very likely to retract between the two leaves of pleura and give rise to a suppurative mediastinitis. Hemorrhage as a rule does not constitute a very real danger unless there is an accidental slipping of a clamp or ligature from the pulmonary artery.

There are two principal methods of operating, one by an intercostal route and the other by a preliminary resection of ribs. Of these the former constitutes by far the more brilliant procedure and, when successful, gives the least deformity; but unquestionably it is also more dangerous. This is the method which has been advocated by Lilienthal and used by him in five cases with two deaths. The other method was used by Robinson in his series of five cases with one death. It is also the method which I used in my successful case. It is a more laborious procedure, but it has many features of safety not possessed by the other method. In the first place it can be done in any number of stages, a fact which makes it more applicable to patients who are not in the best condition. Moreover, it practically insures against the possibility of retraction of the bronchial stump into the mediastinum.

The operation as described by Robinson is essentially as follows: A crescentic incision is used the convexity of which is downwards. It starts at the level of the fifth rib about 2 in. from the vertebral column, crosses the eighth rib in the scapular line and ends at the level of the sixth rib in the mammary line. The skin and fat are turned up and the latissimus dorsi is divided transversely to form part of the flap. Subperiosteal resection of the seventh, eighth and ninth ribs is made from their angles to the anterior axillary line. The intercostal bundles are then ligated and removed. The flap is brought down and sutured in place without drainage. This constitutes the first stage. An interval of a week or more may be allowed to elapse before the second stage. During this time it is hard for the patient to cough up sputum because of the absence of the removed ribs. This will be facilitated by applying a dressing made to fit snugly against the flap by adhesive plaster bands which are long enough to adhere firmly to the skin.

In the second operative stage the flap is elevated and the pleura opened. The diseased lobe is usually adherent not only to the chest wall but also to the pericardium and diaphragm. These adhesions must be carefully separated and will generally require cutting in some places. If the other lobe is not adherent, safety requires that it be made so before proceeding to the amputation. There are two reasons for this, one of which is that respiration will be much less disturbed if the other lobe is fixed, for in that way the usual dangers of a wide open pneumothorax are avoided. The second reason is that the infection of the pleura which is practically certain to follow the lobectomy will not be generalized but will be localized. If the other lobe is found not to be adherent to the chest wall, the diseased lobe after being separated

from the adherent structures is surrounded and walled off by gauze packing, and the wound is closed tight without drainage. This completes the second stage.

On about the third to the fifth day the wound is opened a little in order to let out some of the fluid which has accumulated. It is better, however, to remove the packing only gradually so that it will not be entirely removed before about the tenth day. This delay practically insures the presence of adhesions between the chest wall and the other lobe. New packing must then be carefully replaced. In my own experience, however, instead of replacing the packing I inserted several Carrel tubes and irrigated the cavity with Dakin's solution in order to promote rapid sterilization of the empyema cavity. The third stage should not be undertaken until the cavity is clean. If a long interval has elapsed, it may be necessary at the third stage to separate adhesions which have formed again between the diseased lobe and surrounding structures, but the separation should be easy. At any rate two important objects have been accomplished by waiting, the shutting off by adhesions of the part of the pleural cavity occupied by the unaffected lobe, and the stabilizing of the mediastinum so that the danger of retraction of the bronchial stump is minimized.

The amputation of the lobe may be carried out as soon as the patient is in good condition and the cavity is clean. In my own case, this was done easily and quickly, and the patient had less reaction than after either of the two previous stages. The adhesions all around the lobe are separated and one or two curved clamps are placed on the hilus. The lung is then cut away distal to the clamps. Mass ligatures may be applied or the clamps left on to be removed in from five to seven days. One advantage of leaving the clamps in place is that the bronchial stump is then firmly held and cannot possibly retract into the mediastinal space. The wound is not sutured but the flap is allowed to fall into it. It should not be irrigated because some degree of bronchial fistula is practically certain to occur. The cavity gradually becomes obliterated and is covered with epithelium. The persistence of a bronchial fistula may necessitate a plastic operation for its closure. In my own case complete spontaneous healing occurred.

Concerning the anesthetic, it seems to me that nitrous oxid is decidedly preferable to anything else not only because it does not stimulate bronchial secretion so much as ether, but the added advantage exists, as Gwathmey suggested, that the lungs can be partially inflated by blowing in gas under a little pressure if a snugly fitting face piece is used. This facilitates respiration greatly while working in the open pleural cavity if adhesions are absent between the unaffected as a result of the operation.*

* In an attempt to make the removal of the diseased tissue in cases of chronic suppuration of the lung (both bronchiectasis and chronic lung abscess) safer, I have recently devised another method of operating. This method consists in the removal of the diseased tissue in multiple stages by means of an actual cautery. The reason that the ordinary operation of lobectomy has been associated with a

We have stated here that the only rational treatment theoretically is the removal of the diseased portion of the lung. This is doubtless the only procedure which offers a chance of complete relief in the advanced cases in which the bronchi are so thickened that there is no chance of spontaneous healing. In early cases, however, measures which are less radical than lobectomy often result in remarkable improvement. Every case should be examined for the possible presence of a foreign body. For this purpose not only should the *x*-ray be employed but a bronchoscopic examination should also be made in a search for a non-metallic body. The removal of a foreign body through the bronchoscope is often a comparatively simple procedure which results in marked improvement. Attempts at facilitating drainage by the production of an artificial pneumothorax also often yield striking results. The theory underlying this procedure is that the pressure exerted by the pneumothorax will squeeze the secretions out of the bronchi and will also prevent to some extent their refilling with secretion. It is obvious, however, that only under certain conditions will the use of an artificial pneumothorax be applicable. For its successful application it will be necessary that either the mediastinum be thickened or that adhesions be present which will serve to anchor the lung. Otherwise a considerable amount of pressure will also be exerted on the other lung. However, if the affected lobe is firmly anchored by adhesions it is obvious that attempts to compress it by a pneumothorax will be unsuccessful. In several cases in our experience the production of an artificial pneumothorax not only has failed to effect a compression but has even incited so much pain that the patient has been made much more uncomfortable than he was before. In some recent cases, however, Dr. J. J. Singer and I have seen considerable improvement and in one case the result has been so striking that symptomatically the patient has now been completely relieved for a year and has gained about 40 lb. in weight, although previously she was expectorating from 300 to 500 c.c. of foul sputum every day. The present danger of the radical procedure of lobectomy and the possibility of improvement with less radical procedures makes us feel that perhaps in no case should a lobectomy be performed until after the more simple procedures suggested have been tried. Singer and I have now a series of 20 cases in which various measures have been tried. These cases are being followed in an effort to determine the most rational procedure to be carried out.

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nearly prohibitive mortality is that large areas of raw tissue are exposed to an inevitable infection due to the necessity of first freeing the adherent lobe before removing it. In the operation of pneumectomy with the cautery the part of the lung to be removed does not have to be mobilized first. This diminishes very greatly the amount of infection. In 17 cases I have performed the operation. There have been only two deaths, one due to pneumonia of the other lung and the other one due presumably to an embolism of the brain associated with sudden death after a severe generalized convulsion. The operation is described under the title of "Pneumectomy with the Cautery" in the Jour. A. M. A., lxxxi (1923), p. 1010.

Tuberculosis of the Lung

The surgical treatment of pulmonary tuberculosis has been a disappointment. It has been based largely on two principles, one of which is the direct excision of the diseased portion of lung and the other is the attempted arrest of the process by some one or other of the various methods to produce collapse of the affected lung.

In 1891 Tuffier successfully removed a tuberculous mass from the right apex. Four years later the patient was still in excellent health. Also in 1893 Lowson[166] removed the apex of the right lung for tuberculosis. His patient made a good recovery but died about nine months later from what was thought to be an acute gastric ulcer. The operative removal of a tuberculous portion of lung has never come into common practice and probably it never will, for the simple reason that certainly the majority of cases of pulmonary tuberculosis are bilateral and are therefore not amenable to surgical excision, while the more simple ones with a lesion localized to one part of the lung will frequently recover under suitable hygienic treatment. Large tuberculous cavities with septic absorption have been intentionally drained a few times, and the drainage has afforded some relief from the severe septic symptoms, but, as might have been expected, the tuberculosis continues to run its course and the sinus created for the drainage does not heal. It is a procedure which is not to be recommended. Paget[167] has discussed this whole question rather extensively in his book and has failed to find much support for the operation. Reclus[168] in his address before the French Surgical Congress quotes Taüfert and Werth, who showed that in 100 cases 5 died directly from the operation, 70 lived for only two weeks after it, and 15 less than a month. There were only 10, therefore, who could be considered as being any the better for the treatment and they were given no hope of permanent recovery as a result of the treatment.

Probably the first operation devised with the idea of producing a collapse or compression of a lung was performed by Cayley[169] in 1884. In order to arrest a dangerous hemoptysis in a case of pulmonary tuberculosis, he admitted air into the pleura by an incision in order to accomplish a compression of the lung. The patient died soon afterwards but Cayley felt that the operation had stopped the hemorrhage. It is interesting that the principle should have been rediscovered during the war by Bastianelli who advocated artificial pneumothorax as a means of controlling hemorrhage from lacerated lungs. Ten years after Cayley's operation, Forlanini, before the medical congress at Rome, advocated for the first time the production of artificial pneumothorax as a means of treating pulmonary tuberculosis, not to arrest hemorrhage but to check the progress of the disease itself. Murphy[58] in 1898 advocated the use of nitrogen instead of air because of the delayed absorption of the former. The use of artificial pneumothorax in the treatment of pulmonary tuberculosis is now widespread. It is discussed so fully elsewhere in this System that it will not be taken up here.

Numerous operations have been devised for the purpose of collapsing an affected lung or an affected part of a lung. Friedrich[170] was one of the first to suggest such a procedure; and his operation, or modifications of it, has been performed on a considerable number of cases since its introduction in 1907. The principle of the operation is the extensive resection of ribs for the purpose of creating a collapse of the corresponding lung. Friedrich recommended resection of all the ribs from the second to the tenth inclusive. It is performed through a long crescentic incision of which the convex border is below, and the pleura is not opened. The operation may be carried out in several stages and preferably so because of its formidable nature, especially in debilitated subjects. Local anesthesia is preferable. The selection of cases suitable for such an operation is by no means always easy. It is clear that it is more applicable to cases with a unilateral involvement. In 1911 Friedrich[171] reported 28 cases, in which all but one showed cavities. There were eight deaths and 16 cases with marked improvement.

Friedrich's operation has been revived considerably within the past few years, and now perhaps more interest is being shown in it than at any other time. Meyer[172] has recently reported a case in which he thinks a cure was effected in a young man of 26 who had had symptoms for seven years. P. Bull[173] has performed the operation in 37 cases. His tabulated results follow:

Years	Number	Men	Women	Died	Living, able to work*	Tuberculous	Died later	
							Of pulmonary tuberculosis	Other causes
1914	5	1	4	..	2	..	3	
1915	4	2	2	2	..	..	2	
1916	4	1	3	1	..	2	1	
1917	14	3	11	1	7	4	1	1
1918	6	4	2	..	3	3	0	
1919	4	1	3	..	3	1	0	
Total.....	37	12	25	4	15	10	7	1

* Free from symptoms.

Ochsner[174] states that in 1912 and again in 1920 he had an opportunity to see at Zurich a large number of patients on whom Sauerbruch*

* Sauerbruch's modification of the Friedrich operation has many advantages over the original Friedrich. Sauerbruch has recommended that instead of taking out most of each rib, only a small section (1 or 2 inches) of each should be removed through an incision parallel and close to the spine. The removal of only a small portion of each rib permits an excellent collapse and falling downwards of the whole side of the chest, without, at the same time, subjecting the patient to the marked discomfort which results from having no bony framework over the lung. It is necessary, however, at least to divide the first rib in order to get a maximal collapse of the side.

and later Clairmont had performed this operation. Many of them were entirely well. One cannot yet, however, speak with certain knowledge concerning the efficacy of the procedure because a sufficient number of cases has not been reported. I know of no series of cases in which the operation has been tried in children.

Archibald[175] has suggested another principle in the operative treatment of tuberculosis. Using a method somewhat analogous to that employed by Tuffier in his operation of apicolysis, Archibald has separated the apical pleura from the ribs and has tucked into the space a pedicle of muscle. This procedure is designed to accomplish a permanent compression of the affected portion of the lung. He considers that the indications for the operation should be limited to those cases "of chronic disease with marked tendency to fibrosis, with cavity in the upper lobe and strictly, or almost strictly, unilateral." He has reported two cases in which he has tried the operation. In one an excellent result was obtained, but in the other the ultimate improvement was not so good.

Actinomycosis of the Lung

This condition is so rare that no detailed discussion will be given here. It is common for the pleura to be involved also with the lung. West[176] has reported a case of primary actinomycosis of the pleura in a six year old child. This is said to be the youngest on record. The chest wall was converted into a cartilage-like tissue ¾ in. in thickness. Early diagnosis is difficult, and surgical intervention, therefore, is seldom indicated. Opokin[177] states that eight cases are recorded in the literature in which operative measures of various kinds were followed by recovery. Potassium iodid, copper sulphate and the *x*-ray have all been thought to have a beneficial effect.

Blastomycosis of the Lung

This rare condition is not of very much importance from the surgical point of view. A good many cases of lung involvement have been reported but these have always been cases in which the infection has been generalized. Moreover, I know of no cases of pulmonary involvement in children. One of the first cases affecting the lung was reported in 1906 by Irons and myself.[178] An excellent summary of 22 cases is given by Montgomery and Ormsby.[179]

Echinococcus Disease of the Lung

This is also a rare condition in this country, and moreover its location in the lung constitutes one of its less frequent sites. *X*-ray examination is of the greatest importance, and in typical cases the cyst will appear as a rather sharply outlined spherical shadow. Confirmation may be obtained by the usual physical signs, the eosinophilia and the complement fixation test of Weinberg. Treatment consists in excision, marsupialization or simple incision. The former is the

most satisfactory when it can be done and the latter is the least. Marsupialization frequently results in a complete recovery and is accompanied by a low mortality. Several cases have been described in children. Wilson[180] reported a case in which both lungs of a girl aged six were involved. Graham[181] incised the thoracic wall of an eight year old child who had a bulging on the right side. A large hydatid cyst was emptied and drained, and the child made a good recovery. In another case in a seven year old boy he aspirated 18 oz. of clear fluid from a cyst at the base of the right lung. In another child, five years of age, he found a cyst at the right apex. An unusual case which he has described was in a girl of 11 who had had several attacks of severe hemoptysis. While retching during the last attack she began to choke, becoming "black in the face and insensible. Her mother slapped her between the shoulders and the patient vomited what looked like curdled milk. This was followed by relief and the patient regained consciousness. The vomited material proved to be a large piece of cyst membrane, curled upon itself. When spread out it measured 8 by 4 in." The patient made a complete recovery. O'Conor[182] removed a cyst from the lung of a three year old child who made a recovery. A cyst about the size of an orange was successfully removed from a boy of six by Robinson.[183] Another case of lung involvement in a child is reported by Penrose and Kellock.[184]

Tumors

Tumors of the lung are rare in childhood, and most of those which occur are sarcomatous metastases. Benign primary tumors are exceedingly rare. Schultz[185] reported a fibroma in a child two years of age. Osteomata have been described. Dermoids and teratomata have also been observed, although usually they originate in the mediastinum and invade the lung. The chondromyxomata which arise in the chest wall sometimes invade the lung. Of the malignant tumors sarcoma is the more common. A few cases of supposed carcinoma have been reported in children. One in a girl of seven years has been observed by Nuscheler[186] and a multiple tumor was reported by McAldowie[187] which occurred in an infant of five and one-half months. Horn[188] reported an adenocarcinoma in a girl of 18 years and Werner[189] another case of carcinoma in a girl, 19 years of age. Adler[190] found that in 356 cases of primary carcinoma of the lung six occurred between the ages of 10 and 20. Primary lung carcinoma may arise from the epithelium of the lining of the bronchi, from the bronchial mucous glands, or from the alveolar epithelium.

Of the primary sarcomas the most common type in children seems to be the round-cell. Bjornsten[191] has observed it in a two year old child, Lehndorff[192] in one of three years and Box[193] in a five year old child. These tumors are usually large, often involving all of one lung and pleura in a solid mass. Ewing states that areas of necrosis and large cavities may form, and that metastases are generally local or absent, although there may be extensions to the hilus nodes, ribs and

vertebræ. They differ from lymphosarcoma by their limitation chiefly to the lung.

The symptoms and diagnosis of tumors of the lung vary considerably according to the nature of the growth. Attention may first be directed to the question of tumor of the lung by signs which are frequent also in the common inflammatory conditions. For example: There may be hemoptysis, persistent cough, pleuritic pain, etc. The diagnosis is often impossible, but the *x*-ray will sometimes permit an almost positive diagnosis. Barjon states that three times he made an *x*-ray diagnosis of tumor of the lung when clinically it was not suspected. He gives a very interesting discussion of the whole question of radiologic diagnosis of lung tumors. The shadows produced by tumors of the lung are characterized chiefly by sharply defined contours and in this respect differ from inflammatory lesions. Primary carcinoma is often sharply lobar in distribution and has a tendency to occur more often in an upper than in a lower lobe. Metastatic tumors may show either a nodular or diffuse form. In the former there are usually several shadows which may be limited to one lung or may affect both. Again, the sharpness of contour is the striking feature. The diffuse form may be mistaken for pleural effusion, but it differs from that in the fact that the respiratory movements of the diaphragm are present and there is little or no displacement of the heart and mediastinum. Extensive tumors which have grown to involve the pleura may be associated with a pleural exudate, which in the case of malignant tumors is likely to be bloody. This of course serves to confuse the diagnosis. Suspicion may be directed to a metastatic tumor of the lung if a primary growth elsewhere is recognized; and conversely the pulmonary findings may direct attention to a previously unsuspected primary tumor elsewhere. Exploratory puncture is sometimes of great value in making the diagnosis.

The treatment of tumors of the lung to the present has been unsatisfactory. Black and Black[194] have recently reported a case of teratoma of the lung in a man whom they treated by drainage. He died five months later from hemorrhage. Radical surgical removal has been undertaken in a few cases. In all of the cases of malignant tumor the final result has been poor, but in a few the immediate technical result has been good. One difficulty has been that the cases as a rule are not recognized early enough to give much promise of permanent relief. It is possible, however, that improved methods of diagnosis, by affording an opportunity for earlier operation, may yield better results. In Haidenhein's[195] case in which a lobectomy had been done for bronchiectasis a carcinomatous nodule, the size of a hazel-nut, was found unexpectedly in the wall of a bronchiectatic cavity. Krönlein[196] reported a very interesting case of a sarcoma of the lung, the size of a nut, which he excised from the lung of an 18 year old girl. The tumor appeared twice in the scar and was removed both times. The patient died, however, of extensive metastases seven years after the first operation. Lenhartz[197] successfully performed a lobectomy

for carcinoma of the lung, and the patient survived for 18 months. Excision should certainly not be undertaken lightly, as it is at best an exceedingly severe operation with present methods. Yet it is possible that in the future excision of these tumors will be found to give good results.

The *x*-ray and radium may perhaps accomplish something. But in a recent case of an extensive primary lobar carcinoma of the lung under my care no appreciable result was noted with massive *x*-ray treatment combined with implantation of radium into the growth. Important palliative measures are the withdrawal of fluid from the pleural cavity, when it collects in large amounts, and the relief of pain, which is sometimes extreme.

DISEASES OF THE MEDIASTINUM

Abnormal conditions of the mediastinum are important not only because of the inherent nature of the conditions themselves but also because of the severe effects which they often exert on other very important structures. In no other part of the body except the central nervous system is there offered a similar opportunity for abnormal pressures of the same extent to be developed and resultant serious effects upon important structures.

The most frequent lesions of the mediastinum which are of surgical interest are inflammations and tumors. Occasionally a mediastinal hemorrhage occurs, as a result of trauma, especially of surgical operations on the neck; and although this condition cannot be strictly classified as either an inflammation or a tumor, nevertheless its effects are similar to those of tumor.

Inflammations

Inflammations are either acute or chronic. A simple, nonsuppurative inflammation of the mediastinal structures is probably not uncommon. It is to be supposed that in the majority of instances of inflammation of the pleura or pericardium there must be some accompanying inflammation of the mediastinum. This may result in slight edema, but it is of no surgical significance.

Acute Mediastinitis.—The most important type of inflammation from a surgical point of view is the acute suppurative. The mediastinal tissues are ordinarily thought to possess practically no resistance against infection. While it is true that phlegmonous inflammations seem to occur readily after injuries to the mediastinum, either operative or otherwise, in view of the almost necessary frequency of involvement of the mediastinal pleura in cases of empyema, the lack of resistance of the normal mediastinum must have been exaggerated. The separation of the normal coverings of the structures is probably a factor of great importance in favoring the development of a severe phlegmon, and in this respect these inflammations are similar to those which sometimes occur in the abdomen when the peritoneum has been stripped up from its normal attachments. Nevertheless in any operation on

the mediastinum the very great danger of a severe infection should be borne in mind.

Etiology.—Acute suppurative mediastinitis may occur in any of the following conditions:

1. From injury, especially to the esophagus. Owing to the frequency with which children have foreign bodies caught in the esophagus and trachea, this group forms perhaps the most frequent of the various factors which in children are responsible for acute suppuration in the mediastinum. As a result of the lodging of the foreign body, the esophagus or trachea may become ulcerated through spontaneously, or perforations may occur as a result of instrumental attempts to extract the foreign body. Again, the frequency of esophageal strictures in children as a result of the swallowing of corrosive fluids makes them susceptible to the accident and dangers of perforation from bougies. Mediastinitis occurs also as a result of penetrating injuries, as gunshot wounds, etc., and it has also been known to have followed severe blows on the chest. In the latter instance direct injury may have occurred to the esophagus or trachea which permitted leakage of infected material. The type of inflammation which follows a perforation of the esophagus is usually a very severe, gangrenous phlegmon. As a rule it does not localize into an abscess.

2. As a result of the burrowing of pus downwards from infections in the neck. Phlegmonous inflammations of the neck sometimes extend down into the mediastinum. This is said to be the case particularly with Ludwig's angina. The cases which follow tracheotomy are also of this same general type, but fortunately they are rare complications of tracheotomy. Retropharyngeal abscesses also sometimes burrow down into the mediastinum.

3. As a complication of pneumonia, especially the bronchopneumonia due to hemolytic streptococci. Stone[47] found in the army epidemic that in 100 necropsies substernal pus pockets were present in 11. It should be noted, however, that the pockets of pus which were frequently noted in the army epidemic and often classified as substernal were not always in the mediastinum but were sometimes within a pleural cavity and were therefore really instances of encysted or localized empyema rather than true inflammations of the mediastinum.

4. Secondary to abscesses arising in bone, as caries of the spine or sternum. These conditions of course are usually tuberculous or syphilitic but if the abscesses become secondarily infected they may give rise to an acute suppurative mediastinitis.

5. Rarely in association with pyemia and with the infectious exanthemata of childhood.

6. Rarely as a sequel to gangrene of the lung, sometimes perhaps as the result of the direct extension of the infection.

Pathology.—Acute suppurative inflammation of the mediastinum may be either phlegmonous in type or it may localize to form an abscess. The anterior mediastinum is more commonly involved than

the posterior. In Hare's[198] collection of 65 cases of mediastinitis, 30 were of acute inflammation involving the anterior mediastinum, four of the posterior mediastinum, and both in two cases. The abscesses are sometimes multiple. The amount of pus is sometimes very large. Pleuritis is a common sequel just as it may be also a forerunner of mediastinitis. The abscesses may point in various directions. Those arising in the anterior mediastinum frequently point just to one side of the sternum, and they may ulcerate through the chest wall in an intercostal space and discharge their contents spontaneously. Those arising in the posterior mediastinum frequently point in either the right or left supraclavicular fossa. The abscesses sometimes ulcerate through the esophagus, the trachea, a bronchus, the pericardium or the pleura. Roberts[199] states that in one case an abscess ulcerated into the arch of the aorta and gave rise to fatal hemorrhage. Rarely the pus has burrowed down between the pillars of the diaphragm to point in the iliac or femoral region. As a late result, extensive fibrosis may occur with serious compression effects caused by the contraction of scar tissue around important structures. All sorts of adhesions may form, some of which are of surgical interest. Traction diverticula of the esophagus may also result. These late effects will be discussed more in detail in connection with chronic inflammation of the mediastinum.

Symptoms and Diagnosis.—The symptoms and signs are extremely varied because, apart from the effects of inflammation, phenomena due to pressure on nerves, vessels, etc., become evident. The constitutional disturbances may be those of suppurative inflammation anywhere in the body. In the gangrenous cases, however, the constitutional reaction may be slight. Pain somewhere in the thorax is usually present. It may be indefinitely localized but most commonly it is felt just beneath the sternum which may be tender. If the abscess is pointing externally local tenderness, redness, swelling and even fluctuation may be noted. In large abscesses there may be edema of the anterior part of the thorax and marked dilatation of the superficial veins. This latter phenomenon is said to express an attempt at the formation of a collateral circulation between the superior and inferior venæ cavæ. But the chief effects are not always in the anterior part of the thorax. If the posterior mediastinum is involved the pain may be located between the shoulders or referred along the intercostal nerves, sometimes only on one side. As has already been said in the preceding paragraph, abscesses of the posterior mediastinum often present in the supraclavicular fossæ. Swelling, tenderness and fluctuation may therefore be present in one of those fossæ. Sometimes the abscess pulsates and for this reason may resemble an aneurism. Pulsation is even noted and complained of by the patient in some cases. There may be hoarseness, dyspnea, cyanosis and sometimes hemoptysis. Actual dysphagia is uncommon, although swallowing may be painful. Involvement of the vagus nerves may result in disturbances of cardiac rhythm, gastric symptoms and even vomiting; and if the

phrenics are affected, hiccough, inequality or actual paralysis of the diaphragm may occur.

The diagnosis is often extremely difficult. As a rule, a positive diagnosis can be made only when an abscess is present. The determining features are local and general evidence of suppuration, in addition to the signs of mediastinal tumor. A local area of dulness may be made out by percussion. If an obvious source of the abscess, as a foreign body in the trachea or esophagus, is known, the diagnosis will be easier. If the abscess has already ruptured externally and a discharging sinus is present, the diagnosis will usually be easy. Unfortunately, however, the abscess ruptures less commonly externally and more often into the trachea, the pericardium, the pleura, etc.

The presence of existing complications such as pneumonia, empyema, etc., serves to complicate the picture. In children the conditions which are most likely to be confused with acute suppurative mediastinitis are acute pericarditis with effusion, encysted empyema, lung abscess, hypertrophy of the thymus, new growths of the mediastinum, and enlarged mediastinal lymph glands. Thoracic aneurism which is sometimes difficult to rule out in a suspicious case of mediastinal abscess in the adult is so rare in children that serious consideration of it is not necessary. The presence of severe inflammatory symptoms will of course favor the diagnosis of abscess. The aspirating syringe will establish the diagnosis if pus is found in the mediastinum, but its use is not without danger and other means of diagnosis should be used first.

The *x*-ray is of very great value in establishing diagnosis in these cases, and this fact probably accounts for their relatively greater frequency now than formerly. It is a curious fact that Wilson Fox,[200] with his very extensive experience in diseases of the thorax, states that he has seen only one case of acute inflammation of the mediastinum. Barjon[201] states that "what in general may be considered characteristic of radioscopic examination (of mediastinal effusions) is the fact that the abnormal shadow is always superadded to the median shadow. It deforms and increases this shadow at a point differing according to its location. In the posterior mediastinum it is seen as a dark band adherent to the vertebral shadow and occupying all the inferior part of the thorax from the hilus of the lung to the diaphragm. In the anterior mediastinum, on the right, it is seen as an obscure triangle, the apex of which corresponds to the hilus of the lung and the base to the diaphragm; on the left it is like an enlarged aortic shadow and surmounts that of the heart as in aneurism of the descending portion." Mollard and Rebattu[202] reported a case with a purulent collection which involved the mediastinum anteriorly and posteriorly on the left side. Diagnosis was based on the following considerations: In spite of an effusion which did not seem very abundant, marked dyspnea was present and especially a marked displacement of the heart to the right. It therefore seemed that the fluid—scant in the large cavity—was more abundant and encysted in the

mediastinal region. On the other hand, radioscopic examination showed in the middle of a general obscurity of the left hemithorax, excepting only the apex, a denser shadow visible at first in front, in contact with the compressed heart, then at the same time in front and in back in the mediastinum. A slight evacuation followed by a rather fetid expectoration soon indicated the nature of the collection. After this series of findings the diagnosis was completely and definitely made and soon verified by surgical intervention.

Clinical Course and Prognosis.—The clinical course is variable, depending chiefly on the extent of the inflammation and the type of the infection present. In those cases which are associated with an extensive gangrenous phlegmon death may occur within a few days. On the other hand, some cases recover spontaneously through rupture of an abscess into the esophagus or externally or through gradual absorption. Still other cases run a chronic course. Death from suffocation has occurred from rupture of an abscess into the trachea or a bronchus. Acute inflammation of the mediastinum, however, should always be regarded as a very serious condition with a grave prognosis.

Treatment.—There are two main indications in the treatment: (1) The removal of the cause when that is possible and (2) the establishment of free drainage. Unfortunately it often happens that neither one nor both of these indications can be carried out. A foreign body lodged in the trachea or esophagus should be removed, preferably by means of a bronchoscope or esophagoscope. If, however, an abscess is already present, it should be opened and free drainage instituted. If the abscess is already pointing it should be opened at that place; otherwise some doubt may exist as to the best site through which to gain access to it. If pointing occurs at one side of the sternum, an incision should be made there and the opening enlarged sufficiently to get adequate drainage. With a finger in the abscess cavity as a guide, one or more costal cartilages, portions of one or more ribs and even some of the sternum may be removed. The most important consideration is to accomplish satisfactory drainage. If the abscess is not pointing but its location has been recognized as in the anterior mediastinum, the sternum may be exposed and trephined. Through the trephine opening the needle of an aspirating syringe may be passed to locate the pus. It is interesting that Galen trephined the mediastinum for a mediastinal abscess. In 1768 Lamartinière[203] wrote a treatise entitled "Sur l'Opération du Trépan sur le Sternum" in which he quoted antecedent writers. Particular care should be exercised to see that important structures are not injured in the drainage. If tubes are employed they should be well protected by gauze. In cases of phlegmonous inflammation without abscess the treatment is less satisfactory. Application of heat or cold over the sternum will sometimes relieve the pain somewhat. If associated with a phlegmon of the neck extensive incisions should be made in that region. Phlegmons of the neck, however, frequently lead to abscesses in the posterior mediastinum.

The posterior mediastinum was attacked surgically at a much later period than the anterior, and fewer cases of surgical intervention in this region have been recorded. Lerche,[204] in a recent article, states that he could find in the literature only 10 cases reported in which suppurative processes in the posterior mediastinum had been drained. These cases included those of Luermann[205] in 1876, of Ziembicki[206] in 1895, of Obalinski[207] in 1896, of Cavazzani[208] in 1899, of Heidenhain[209] in 1899, of Rasumowski[210] in 1900 and of von Hacker[211] in 1901. Gaudiani[212] in 1916 published two cases. To the 10 cases published in the literature Lerche has added one of his own. It is very striking that only 11 cases altogether have been recorded in which acute suppuration in the posterior mediastinum has been subjected to surgical intervention, and it is an interesting commentary on the very undeveloped condition of thoracic surgery at the present time. In Obalinski's case only an abscess in the neck was drained, and the mediastinum was not operated on, although at necropsy pus was found in the posterior mediastinum. In reality, therefore, only 10 cases can be considered as having been treated surgically. In this number there were only three deaths. A recovery of 70 per cent. by operation in this class of cases seems remarkably good when one considers the extreme gravity of the condition and its almost hopeless outlook when untreated. This record seems good also because almost entirely it is a record of single cases treated by different surgeons. Additional experience gained by more frequent operating on such cases will doubtless reduce the mortality still more. The modern advantage of the *x*-ray will unquestionably lead to more frequent recognition and operation in these cases.

In general two methods of approach to the posterior mediastinum have been recommended, the cervical and the dorsal. Cervical mediastinotomy may be performed on either side of the neck. The recognition of a cervical phlegmon or the presence of a discharging sinus will of course indicate on which side the incision is to be. Torek[213] has recommended that, in case of doubt as to which side, the patient be placed with the head lowered in the Trendelenburg position for a day or two; an area of redness will then sometimes appear over one clavicle indicating on which side to operate. The incision may be made parallel to the clavicle, dividing the clavicular attachment of the sternocleidomastoid muscle or parallel and anterior or posterior to the muscle. On the left side Heidenhain has advised going down into the thorax on the lateral side of the carotid artery and jugular vein, and on the right side choosing a cousre between them. Von Hacker has recommended going down on the mesial side of the vessels. Lerche operated through an incision parallel to the right sternocleidomastoid muscle. The operation was performed in 1907 with a complete recovery. In 13½ years following it (the time of making his report) there had been no further trouble. Although the case was an adult, it presents so many interesting features that I quote the description of it at length:

On Aug. 26, 1907, I examined Mrs. R. T., age 50 years. She had had a dry catarrh of the nose and throat for many years. For six years preceding the examination the patient had had a peculiar, hard, metallic cough, which frequently became paroxysmal in character. For about the same length of time she had had periodical attacks of dysphagia in which food would stick in the gullet, so that she had to force it down with liquids. There had been no regurgitation, but she had suffered severe pain behind the lower part of the sternum before food passed into the stomach.

In the last few months prior to the examination, the attacks had increased greatly in frequency and the last one had been of several weeks' duration. She had to limit herself to liquids and even those would cause much pain behind the sternum. She had lost 10 lb. in weight.

Examination showed an atrophic rhinitis, and the pharynx had a dry, glazed appearance.

The esophagus was empty but somewhat dilated and the epicardia-cardia was seen in spasm in one of the three esophagoscopies made. The cervical part of the esophagus had the same dry, glazed appearance as the pharynx, the dysphagia and the spasms of the esophagus gradually grew worse, and on October 5 the patient had a temperature of 102 degrees and pulse 110, with swelling and tenderness of the lower right side of the neck. October 7 small quantities of pus were gulped up.

October 8 an incision was made 10 cm. in length along the anterior border of the sternocleidomastoid muscle to the sternal notch. When the right lobe of the thyroid was retracted toward the mid-line, a large abscess cavity was disclosed behind it, between the esophagus and the trachea on the inner side and the sternocleidomastoid muscle and the large vessels on the outer side.

The abscess could be followed into the superior and posterior mediastinum for about 9 or 10 cm. below the top of the sternum. A rubber drainage tube was left in the mediastinum, the rest of the abscess cavity packed with iodoform gauze, and the patient put to bed in Trendelenburg's position. The following day a siphon drain was arranged with the patient in the horizontal position. Later a soft rubber bulb was attached to the drainage tube, which the patient now and then adjusted for suction. The wound healed in seven weeks.

Although there were small quantities of pus gulped up the day before the operation, there was at no time any evidence of esophageal fistula.

This case is of remarkable interest. It seems hard to account for the presence of symptoms of mediastinal irritation for six years culminating in an acute abscess of the posterior mediastinum, which recovered completely after drainage. The abscess could probably have been definitely recognized if an *x*-ray examination had been made. The simple suction device used to facilitate drainage is an important point in the treatment. The burrowing of the pus in the groove between the trachea and esophagus is also of interest. In many of the reported cases the pus was found behind the esophagus. Lerche carried out some experimental injections on the cadaver which throw some light on the course taken by pus from the neck into the thorax. I quote again from his article: "In order to get information about the probable route taken by a liquid mass introduced into the upper part of the groove between the esophagus and trachea, I injected into that area, in fresh cadavers, barium suspended in buttermilk. With moderate, gradually increasing force, the liquid mass was found to extend laterally along the esophagus and trachea into the superior mediastinum, extending a few centimeters below the tracheal bifurcation into the posterior mediastinum. It also followed the vessels, and

when greater force was used, it crossed in front of the trachea to the opposite side."

Of the seven cases in the literature in which there was recovery after drainage, in six operation was by cervical mediastinostomy alone. In the other case, that of Cavazzani, dorsal mediastinostomy was added after three months of drainage by the cervical route.

Dorsal mediastinotomy is indicated in cases in which the abscess is too low to be reached by the cervical method and also in those cases in which experience shows that adequate drainage cannot be obtained by the cervical route. In the latter group the drainage, therefore, will be obtained by utilizing a combination of the cervical and dorsal routes. Dorsal mediastinotomy is a more formidable procedure and will probably be accompanied by a higher mortality than cervical drainage. Entrance to the mediastinum may be obtained on either side of the spine but important structures are present on both sides. On the left side the large vessels are in danger of injury, and on the right side the pleura is hard to avoid. If there is positive evidence that the abscess is pointing to one side of the spine, obviously that side should be chosen. Rehn[214] and Quénu and Hartmann[215] have devised very similar operations for access to the posterior mediastinum, but they differ in that Rehn has preferred the right side and Quénu and Hartmann the left. In Rehn's operation a longitudinal incision is made midway between the spinous processes and the mesial border of the right scapula. Subperiosteal resection of a portion of one or more ribs is made close to the transverse processes of the vertebræ. The intercostal muscles, nerves and vessels are divided. In going into the posterior mediastinum care is used to keep close to the lateral surfaces of the bodies of the vertebræ in order to minimize the risk of entering the pleura; at the same time the sympathetic nerves, the right vagus and the azygos must be carefully avoided. Heidenhain has suggested an operation which entails less risk of injuring the pleura because it allows the operator to keep closer to the mid-line. The operation is sometimes known as costotransversectomy. The incision is close to the mid-line. After resecting the soft parts from the arches of the vertebræ the transverse processes are resected with bone-cutting forceps and a small portion of one or more ribs is resected subperiosteally to a distance just beyond the tubercles. After dividing the periosteum the finger can then push aside the pleura and enter the mediastinum. If an abscess is present, it should be found readily. In dorsal mediastinotomy the esophagus can usually be examined readily. Since a considerable number of abscesses are a result of leakage from the esophagus, search should be made for such a lesion if it can be made safely. Necrotic bone from vertebræ may also be recognized in this way.

Chronic Mediastinitis.—The late effect of pyogenic infections of the mediastinum is a fibrosis which sometimes has serious results because of the importance of the organs involved in the scar tissue. As a rule, the changes are more pronounced in the anterior medastinium,

and in a considerable proportion of cases they are limited to that region. There may be only a few adhesions between the pericardium and the chest wall, or, on the contrary, they may be so numerous and extensive that at necropsy it is difficult to distinguish one organ from another. The clinical features are subject to considerable variation, depending on the particular structures involved and the extent to which they are involved. The large veins (superior vena cava, pulmonary vein, etc.) are especially likely to be involved. Hemorrhagic infarcts were found in the lungs of all of Kussmaul's[216] cases, and the pseudocirrhosis of the liver in association with adherent pericardium, as described by Pick, is now well known. The most characteristic clinical and pathologic picture is present in those cases in which there is an adherent pericardium. This seems also to be about the only syndrome which surgical interference can hope to improve. A detailed consideration of the surgical treatment will be reserved for the discussion on pericarditis.

Another type of chronic inflammation of the mediastinum is that of tuberculosis, syphilis, etc., of the mediastinal lymph glands. Tuberculosis of the thoracic duct has also been described which sometimes results in perforation. Tuberculous inflammation of the glands sometimes gives rise to the formation of a cold abscess in the mediastinum. Usually these conditions are of no special surgical significance because they are part of a more extensive involvement, particularly of the lungs in the case of tuberculosis. Enlarged mediastinal glands are sometimes mistaken for new growths, and the differential diagnosis may be exceedingly difficult. Search for an etiologic factor for the possibility of enlarged glands, as, for example, tuberculosis, will often give the necessary clue for the differentiation.

In Hodgkin's disease the mediastinal glands frequently become greatly enlarged and cause various pressure effects. Radical surgical intervention on the mediastinal glands in this type of case is not indicated, and so far as I know it has never been attempted. *X*-ray therapy will usually result in a very marked reduction in the size of the glands, although probably a recovery from the disease by this method of treatment cannot be expected.

Emphysema of the Mediastinum

The accumulation of air in the mediastinum seldom occurs in sufficient amounts to be of great significance, but sometimes it may produce very alarming symptoms and even death. It is almost always traumatic in origin and results from injuries to the air passages or to the esophagus; occasionally it has followed operations on the neck. Usually the extravasated air disappears within about 24 hours. The symptoms produced are chiefly those of pressure; and complaint is made of a sense of sufiocation. Surgical intervention is almost never indicated for the relief of the emphysema, but if the symptoms should become so alarming that life seems to be threatened, a cervical mediastinotomy might help to relieve pressure, or a resection of ribs or

sternum might be carried out. If instead of being due to air, the emphysema results from gas formed by some of the various gas-producing anaërobic bacilli, the prognosis is practically hopeless.

Tumors of the Mediastinum

Under this heading will be discussed not only new growths but also hypertrophy of the thymus. True new growths of the mediastinum are comparatively rare in childhood. Even those supposedly of congenital origin, like dermoid cysts and teratomata, are not usually of sufficient size to be clinically recognizable until adulthood is reached. In a general way the mediastinal tumors may be classified as malignant and benign.

Of the malignant tumors, carcinoma in the adult is fairly frequent, sometimes as a primary tumor originating in the epithelial structures of the posterior mediastinum, the esophagus, trachea, bronchus, etc., and sometimes as an extension of carcinoma involving the chest wall or as a metastatic growth from some other source In children, however, obviously this tumor is so rare as to cause doubt about the correctness of the diagnosis in reported cases.

Sarcoma of the mediastinum occurs with some frequency in children. Various forms are encountered, such as round-cell, spindle-cell and lymphosarcoma. According to Hare practically all sarcomata of the mediastinum are primary. Even when the growth is extensively disseminated from a primary tumor elsewhere the mediastinum usually escapes, but not always. Hare states that "where the disease is primary in an arm, the secondary growth not infrequently occurs in the mediastinum, comparatively speaking, while sarcoma in the leg, as a general rule, attacks secondarily the abdominal viscera rather than the tissues above the diaphragm." It is doubtful to what extent this rule holds true. I have seen exceptions. As to the origin of sarcoma of the mediastinum, the lymphosarcomas arise from the mediastinal or tracheobronchial lymph glands and from the thymus. Ewing[217] states that "most of the mediastinal lymphosarcomas arise from the thymus and are to be considered as varieties of thymoma." Schlagenhaufer[218] and Kundrat[219] have each reported two cases of lymphosarcoma apparently arising in bronchial lymph-nodes with extensive invasion of the wall of the esophagus. Other sarcomata have arisen in the periosteum of the sternum, in the pleura and in the subpleural tissue with encroachment upon the mediastinum Roberts[220] states that the latter seem to be not uncommon in very young children. It would seem to the writer that considerable difficulty might be encountered in distinguishing between tumors arising in the pleura and those arising in the subpleural tissues.

The tumors which arise in the thymus are in some respects different from any which are found elsewhere in the body. They have also given rise to much confusion as to classification and interpretation.

Ewing[217] has carefully studied this whole question and has brought it up to date. For that reason I quote extensively from him:

"Thymic tumors fall into two main groups:

1. Lymphosarcoma or thymoma, composed of a diffuse growth of round, polyhedral and giant-cells. The chief source of this tumor is probably the reticulum cell, but lymphocytes are often present in abundance.

2. Carcinoma arising from the reticulum cells.

"To these may be added very rare and somewhat questionable cases of tumors attributed to the stroma and called (3) spindle-cell or myxosarcoma.

"Owing to the uncertainty which still surrounds the nature of the thymic round-cells, the term 'thymoma' has been suggested by Thiroloix and Debret, Simmonds, and others, for tumors of this origin, while Schridde employs the phrase 'malignant thymus tumors.'

1. Lymphosarcoma or thymoma is the most frequent form of thymus tumor. The tumors occupy the anterior mediastinum in the position of the thymus, and usually extend from the sternal notch, or as high as the thyroid, down to the diaphragm. There is little difficulty in distinguishing thymic tumors at autopsy from tumors of mediastinal lymph-nodes, lung or sternum. They usually surround and compress the trachea, bronchi, pericardium and great vessels. Both by compression and less often by invasion of vessels and air passages, they cause death by asphyxia and venous obstruction. The more rapidly growing tumors are soft, but as a rule they are found to be remarkably dense from diffuse fibrosis. The soft tumors may be vascular and hemorrhagic while the firm growths exhibit a characteristic lobulation from dense fibrous septa. Rarely areas of softening and cyst formation are observed. In many cases the tumors exhibit a characteristic creamy yellow or lemon color.

"A strict encapsulation within the mediastinum has been a notable feature in some histologically malignant growths, but the more malignant forms regularly become adherent to surrounding organs, and invade pleura, lung, pericardium, walls or lumina of vessels and trachea. The bronchial and cervical nodes are frequently invaded. The axillary nodes may early be enlarged. Tumors of the axillary nodes without known origin should call for the investigation of the thymus by the *x*-ray, especially before any operation is attempted on the axilla. Occasionally there are metastases in the organs, spleen, liver, adrenal, pancreas and kidney (Zniniewicz). Perforation of the chest wall has occurred in several cases and was the first localizing symptom in a case I have recently observed (Seebohm, Zniniewicz, Le Tulle). Fracture of the humerus from bone marrow metastases is recorded by Zniniewicz and infiltration of the orbits, brain and other organs by Meigs and de Schweinitz.

"The structure of these tumors varies greatly. Exactly the same difficulties are encountered in their histological classification as one meets with in tumors of lymph-nodes. In one group the structure

resembles that of an infectious granuloma of the type of Hodgkin's disease. The tissue presents lymphocytes, plasma cells, and larger polyhedral cells irregularly distributed. Several cases of this type have been recorded, with emphasis on the presence of many large polyhedral or giant cells (Ertman, Weigert and Laquer). These large cells must be derived from the reticulum. When they become very numerous the lymphocytes largely disappear and the tumor may be classed as a carcinoma, as has commonly been done by French writers (Le Tulle). In another group the reticulum cells are said to be missing and the tumor is composed of a diffuse growth of small round cells (Le Tulle, Stockart). These tumors have not been distinguished from other lymphosarcomas, but it does not appear that any definite effort has been made to do so. The existence of a pure lymphocytoma of the thymus apart from leukemia does not appear to have been established.

"The blood vessels may be very numerous and in some cases cells of medium size may form sheaths about the vessels. When the perivascular arrangement becomes very marked and lymphocytes are scanty the diagnosis of endothelioma or perithelioma may be suggested, as in the case of Hahn and Thomas, and Mandelbaum and Celler.

"On close analysis the round-cell tumors of the thymus are found to differ in structure from the round-cell tumors of lymph-nodes. The lymphocytes are scanty. The chief cell showing mitosis is often polyhedral, with acidophile cytoplasm, vesicular nucleus and well-developed nucleoli. They often cling to the walls of numerous small capillaries where they assume a cubical or even cylindrical form. They may produce abortive Hassall's corpuscles. The giant-cells are of two main types: (1) Pale staining reticulum cells with irregular outlines, distended with vacuoles and red cell detritus, and (2) myeloid giant-cells with opaque acidophile cytoplasm and many vesicular nuclei. These giant-cells differ from the smaller giant-cells of lymphatic Hodgkins' disease."

The group designated as carcinoma will not be discussed in detail here because it does not occur in children. Of the third group, the thymic sarcoma, Ewing states: "Although it has been commonly assumed that various spindle-cell or alveolar or perivascular tumors arise from the connective-tissue stroma of the thymus, this origin has never been fully traced and there are strong grounds for concluding that the so-called spindle-cell sarcomas and endotheliomas are varieties of thymoma. Congenital myxoma, 10 by 8 cm. in dimensions, weighing 182 gm., containing lymphocytes and Hassall's corpuscles in the tumor-tissue, was observed by Caso in an infant of two and one-half months, and a similar case is described by Winogradoff."

As an evidence of the great confusion which exists about the interpretation of these tumors of the thymus Ewing states that "it is significant that the carcinomas have been recorded almost entirely by French observers, while practically all the German reports are of sarcoma." As to their ultimate nature he has advanced a considerable

amount of evidence which indicates that most tumors of the thymus represent infectious granulomas or particularly forms of cell overgrowth arising on the basis of an infectious granuloma.

There is another indefinite condition to which Sternberg[221] has applied the name "leukosarkomatose." The cases grouped by Sternberg under this name show the features of an acute or subacute leukemia with tumor-like masses in various places. He considered chloroma, or chlorosarcomatosis, as constituting one type of this condition. But there are also similar types of leukosarcomatosis in which the tumors have no green pigment. A considerable number of cases of this latter type have been reported in which there has been a tumor of the thymus gland with the blood picture of leukemia. These are prone to develop in young individuals. Cases of this kind have been reported by Mager,[222] by O'Kelly[223] and recently by Weber and Wolf.[224]

The clinical course of tumors which arise in the thymus is in general a rapidly progressive one. Ewing states that Ambrosini's five cases were all fatal in from two to nine months. Hahn and Thomas[225] have reported a case in which the tumor grew within one year to a size of 26 by 18 by 9 cm. An interesting relationship has been found to exist between tumors of the thymus and myasthenia gravis. Oppenheim[226] states that Weigert was the first to describe the cell infiltration of the muscles in this disease and to trace it to a tumor of the thymus. Since then this relationship has been found to exist repeatedly. Mandelbaum and Celler[227] found lesions of the thymus recorded in 11 of 45 reported cases of myasthenia. In some cases the lesions of the thymus were considered to be a simple hyperplasia but in others the tumor has shown the structure of a lymphosarcoma. Usually the tumors are not large. Not only in the skeletal muscles but also in the various viscera collections of lymphocytes are often found with polymorphonuclear leukocytes, eosinophil, plasma or epithelioid cells.

Treatment.—Since the majority of the tumors which arise in the thymus are malignant, it is probable that, from a theoretical standpoint, the only hope of a complete cure would lie in an early radical extirpation. On the other hand, it is possible that successful results may be accomplished by *x*-ray or radium therapy. The present difficulty in diagnosis makes one hesitate to recommend an operation in suspected cases, because doubtless many would be subjected unnecessarily to an operation unless one delayed until unmistakable signs were present and thereby lose the opportunity to effect an easy extirpation with more certain results. So far as I know, an operative extirpation has never been attempted deliberately in a malignant thymoma, but certainly in the future some of these cases will come to operation. Gaudier[228] operated on an infant of 10 months for severe dyspnea which was supposed to be due to a simple hypertrophy of the thymus. The child was moribund at operation but a subtotal thymectomy was performed, followed by death on the third post-operative day. At necropsy a large mass of thymus tissue was found still to be present which was diagnosed microscopically as a

sarcoma. Apparently this is the only case of primary tumor of the thymus in the literature which has been subjected to operation. Foot[229] has recently reported the case of a nine year old child with a thymoma who died just as an operation was to be performed for a supposed mediastinal abscess. It is doubtful how much could be accomplished by operation in these cases because the majority of them pursue a rather rapidly fatal course. The attempt should be made, however, in enough of them to provide information as to what sort of operative results might be expected. The great difficulty consists in making the diagnosis at a stage early enough in the disease to permit the possibility of a complete removal of the tumor. There is no clinical means of distinguishing with certainty between a simple enlargement and a malignant tumor of the thymus unless the latter is advanced. As regards the treatment of these tumors with the *x*-ray or radium, very little that is certain can be said. Zum Busch[230] has reported a case of complete disappearance of a supposed sarcoma of the mediastinum. Roberts in his article published three years later stated that he had had a recent opportunity to examine the patient and had found the result to be still satisfactory. Other successful results of *x*-ray treatment of mediastinal tumors have been reported by Clopalt[231] and by Schwarz.[232] The difficulty with these cases, however, is that the diagnoses were only clinical.

If an operation is decided upon, two methods of approach suggest themselves, one through an incision in the neck and the other through the sternum. Olivier[233] and also Veau,[234] who have both had an extensive experience in thymectomy for simple hypertrophy, advise a longitudinal incision in the mid-line just above the top of the sternum. The superficial fascia is divided longitudinally, as is also the middle cervical fascia between the sterno-thyroid muscles. These muscles are then retracted and on expiration the thymus is seen to ascend above the upper level of the sternum unless it is fixed by adhesions. It may then be seized with forceps, the capsule opened and a partial thymectomy performed. The operation is practically bloodless if care is taken to keep in the mid-line. I have performed this operation a number of times in young animals and have found it to be exceedingly easy. It is practically impossible, however, to remove all of the thymus by this method. For malignant thymomas, therefore, it would not seem to be a feasible operation. Instead a method which would involve splitting the sternum would probably be required. Such a procedure is described below in connection with the treatment of mediastinal dermoids and teratomata.

Dermoids and Teratomata.—Another important group of tumors of the mediastinum are the dermoid cysts and teratomata. These are not nearly so common as the groups of tumors described above, but yet they are being recognized with increasing frequency. In most of the clinical reports no distinction has been made between true dermoids and teratomata, although from the standpoint of origin pathologists usually confine the term dermoid to those tumors which contain

elements derived only from the epidermal layer, such as hair, sebaceous material, teeth, etc. On the other hand, the term teratoma is usually reserved for those tumors which contain elements derived from all three embryonic layers, such as bone, cartilage, nervous tissue, intestine, respiratory ciliated epithelium, etc., in addition to the epidermal structures found in true dermoid cysts. Ekehorn[235] concludes that most of the reported mediastinal dermoids are really teratomata. Ewing states that most authors are in agreement that the dermoids are derived from the third branchial arch which produces the deep sinus cervicalis and the thymus. Dermoids of the lower mediastinum, however, may result from imperfect closure of the anterior chest wall. Bergmann[236] saw a dermoid divided into two compartments by the sternum but joined by a canal through the bone. In general these tumors are benign, but, according to Ewing, malignant changes have been observed in three cases. Such an occurrence has recently been reported by Ceelen.[237]

The most complete recent article on the subject of dermoid cysts and teratomata of the mediastinum is by Hertzler,[238] who gives a very extensive bibliography. I shall take occasion to quote extensively from his article which reviews 72 cases collected from the literature in addition to one of his own.

They are found most frequently in young adults; but of the 73 cases reported, four were found in children under 10 and four were also present between the ages of 10 and 20. They are about equally divided between the two sexes.

Considerable variation in relationship to other structures is encountered. Hertzler found, for example, that in seven cases the tumor was connected with a bronchus. In 12 cases it was adherent to the pericardium or pleura. In nine cases it was attached to a lung or protruded into the pleural cavity; and in 11 cases the mass extended into a lobe of the lung. Attachment to the diaphragm was present in 11 cases and to the large vessels in four cases. In one case the tumor was adherent to the chest wall.

Symptoms and Diagnosis.—The symptoms and physical signs are chiefly those of pressure produced by the presence of a tumor. Cough is a very common symptom. Dyspnea was noted in 23 of Hertzler's cases (31 per cent.). In three cases death occurred in dyspneic attacks. Pain is of relatively uncommon occurrence. Dysphagia was present in only three cases. Only one case of vocal-cord paralysis has been recorded. It frequently happens that signs of irritation and inflammation appear in the tumor. Hertzler has emphasized the similarity in this respect between these tumors and wens. Hertzler states that the coughing up of hair and the characteristic contents has led to a positive diagnosis more often than any other factor. Hair has been recognized in the sputum in eight cases. On physical examination the evidence of tumor is usually obtained by the abnormal dulness. In eight cases this dulness extended laterally to the borders of the sternum and in nine instances it extended above the upper border of the

sternum or above one or both clavicles. There is often a visible fullness and swelling above the sternum. This frequently imparts a boggy sensation on palpation which is fairly characteristic. In several cases anbormal dulness extended over a considerable area of the side of the chest, reaching the lateral wall at or below the angle of the scapula. This is a strongly presumptive sign but it has often led to confusing it with that of pleural effusion. A number of these tumors, therefore, have been aspirated and a diagnosis made by recovery of the characteristic thick grumous material. Some have even been operated on under the mistaken diagnosis of empyema. The characteristic contents and the polypoid masses growing into the tumor readily reveal its nature.

The *x*-ray is of the greatest value. A shadow of a non-pulsating spheroidal tumor is often obtained which, in the presence of other symptoms and signs enumerated above, makes the diagnosis practically certain.

Treatment.—Surgical treatment only can accomplish complete relief. Theoretically, of course, the ideal method would be extirpation of the entire tumor with its wall. Practically, however, this is seldom feasible because of the technical difficulties encountered which would jeopardize important structures. In three cases in which von Eiselsberg[239] attempted excision of the whole tumor, one died from secondary hemorrhage and another from pericarditis. Bastianelli[240] successfully extirpated one from the anterior mediastinum at a secondary operation. Souligoux states that Morestin, Bergmann and Madelung have also each extirpated one. In general, the most that can be done is incision and drainage with removal of the polypoid masses. In the series collected by Hertzler, including his own case, 28 were operated on. In six cases there was complete recovery and in 13 marked improvement. In four cases the result was indeterminate or not stated, and in five death occurred as the direct result of the operation. Nondrot,[241] however, states that of 22 collected operated cases 16 were markedly improved (70 per cent.) and seven were definitely cured without fistulas. Hertzler's own patient made a complete recovery. In many cases a discharging sinus results which is more or less permanent. Partial extirpation of as much of the wall as possible, removal of the contents and drainage have given good results in a few cases.

Access to the tumor is usually easy since the majority are situated in the upper part of the anterior mediastinum. They may be reached frequently from the neck as is the case in thoracic goiter. It may be necessary to divide the sternal and clavicular attachments of the sternocleidomastoid muscle to get suitable exposure. An incision parallel with the upper border of the sternum and the clavicle will usually be found to give all the exposure required for evacuation of the contents and removal of the polypoid masses, particularly if the sternocleidomastoid muscle is divided. If the more radical operation of extirpation is to be attempted, it will probably be safer to divide the sternum. This may be done by making a vertical incision down the middle of the sternum from the cervical incision. With a chisel the

sternum may then be split longitudinally down to about the third or fourth rib. With the chisel the sternum may then be cut transversely at about the level of the lower part of the incision, and the costal cartilages divided; each half of the sternum is then reflected backwards, thus exposing the mediastinum. This method of approach is one which was used by Lilienthal[242] in a case of a large intrathoracic goiter. It had been previously described by Sauerbruch.[243] A method nearly identical with it had been described in 1906 by Basch[244] in animal experiments.

It is possible that after the contents of the tumor have been evacuated, deep *x*-ray therapy or the direct application of radium may assist in the destruction of the lining epithelium. The application of radiotherapy would be facilitated if a portion of the sternum were permanently removed. This procedure furthermore would result in decompression in a manner similar to decompressive operations on the skull. By diminishing pressure it would also probably relieve pain and prolong life.

Other tumors involving the mediastinum which occasionally occur in children are thoracic goiters and the very rare lipomas and fibromas. In a recent article on substernal and intrathoracic goiters Pemberton[245] has analyzed 25 intrathoracic goiters at the Mayo Clinic. The youngest patient was 15 years old. Fitz[246] in 1905 reported a large mediastinal lipoma associated with a congenital hypoplasia of the left lung. In his article he discusses the literature of mediastinal lipomas.

ABNORMAL CONDITIONS OF THE THYMUS

Tumors of the thymus have been discussed above in connection with mediastinal tumors. Certain additional conditions involving the thymus which have some surgical interest will be briefly discussed. Chief of these is hypertrophy.

Normally the thymus is present only during early life. It increases in size up to the age of about two or three years, remains stationary until about the twelfth year and then undergoes atrophy so that at about the twentieth year either only a trace or none at all of it is left. Occasionally, however, it persists to advanced age in a person who has had an average sort of existence. Claude[247] found a well-defined thymus as late as 94 years of age. Waldeyer[248] concludes that it never completely atrophies but that throughout life it retains something of its old form, and preserved within its substances there may always be found remains of the original thymus tissue. The weight of the organ at birth is subject to great variation. Sappey[249] gives it as 2 to 3 gm. and Testut[250] as 6 to 12 gm. During the first five years of life it does not change materially in size or weight.

At present the functions of the thymus are unknown. Its interesting cycle of development during the period of greatest growth of the body suggests that it must have an important bearing on growth. The experiments of numerous investigators, Friedleben,[251] Basch,[244] Matti,[252] and particularly of Klose and Vogt[253] seemed to indicate that

such was the case and especially that the thymus exercised a profound influence on the growth of bone. Recent studies, however, of Park and McClure[254] have caused serious doubt to be cast over the correctness of the interpretation of the results obtained by the earlier investigators. These latter observers have shown in a very convincing manner that the results reported by the earlier writers mentioned, and attributed to the effect of the removal of the thymus, could be duplicated precisely merely by keeping young pups in close confinement without any operation on the thymus. They found also that, contrary to the other results, the thymus is not essential to life in the dog and that extirpation of it produces no detectable alteration in the hair, teeth, contour of the body, muscular development, strength, activity or intelligence of the experimental animal. Also its extirpation does not retard growth or development. They felt, however, that they could not exclude absolutely the possibility that its extirpation may retard closure of the epiphyses. An excellent discussion of the literature on experimental extirpation of the thymus is given in this article. There is also an exhaustive bibliography in the article of Klose and Vogt.[253] The interesting experiments of Gudernatsch[255] showed that the feeding of thymus to tadpoles causes a great increase in the rate of growth while it suppresses the developmental changes, an action which is the opposite to that produced by thyroid feeding.

Enlargement and Hypertrophy

The observation is old and well known that not infrequently a condition of alarming or even fatal dyspnea is associated with an enlargement of the thymus. It has been generally felt that this is largely a pressure effect, and naturally enough the idea occurred of relieving the dyspnea by removing the thymus. It was largely with this idea in view that the operation of Olivier[233] and of Veau[234] were devised for thymectomy. The former states in his monograph that up to 1911, 39 thymectomies had been performed because of severe dyspnea. Of this number cure was said to have been obtained in 24 and there were 15 deaths. Of these 15, five were due to infection produced by drainage or a tracheotomy, four were caused by a mistake in confusing enlarged tracheo-bronchial glands for an enlarged thymus, three to the desperate condition of the patient at the time of the operation, one to bronchopneumonia 18 days after the operation, one to diarrhea a month after the operation and one to an unknown cause. It is very doubtful, however, whether the operation will have a large application for the simple reason that the *x*-ray will produce a rapid disappearance of a simple hypertrophy of the thymus. One of the first successful cases of this nature was reported by Friedländer[256] in 1907. Aubertin and Bordet[257] in 1909 also called attention to the striking effect of the *x*-ray on the thymus, and more recently it has been discussed in an article by Regaud and Cremieu.[258] Despite the beneficial effects of the *x*-ray, however, it is not unlikely that in some

FIG. 44.—Very large thymus from a boy dying four hours after birth. The thymus filled the larger part of both sides of the thorax. (After H. Klose, Chirurg. d. Thymusdrüse, F. Enke, Stuttgart.)

FIG. 45.—Asphyxia in hyperplasia of the thymus. Sinking in of anterior neck region. Contraction of auxiliary muscles of respiration. Drawing in of lower thorax on inspiration. (After H. Klose.)

cases the simple procedure of partial thymectomy described by Olivier will be applicable because of the urgency of the symptoms present, especially since no appreciable effect from the *x*-ray could be expected in less than several days.

Closely allied to the simple enlargement or hypertrophy of the thymus is the vague condition generally known as "status lymphaticus," or "status thymicolymphaticus," which was originally described and emphasized by Paltauf[259] in 1889. Although this condition has been very extensively investigated, very little is known about it even yet. It is important surgically because sudden death occurs rather commonly as one of its most striking features, and the death may result from what is apparently a relatively trifling incident. Deaths occurring during the course of a general anesthesia, particularly with chloroform, or during minor surgical procedures have often been attributed

FIG. 46.—Intrathoracic goiter successfully removed by author.

to this condition. Many of these, however, can be explained without invoking the mysteries of the very indefinite condition of status lymphaticus; but yet other deaths occur suddenly for which no ready explanation is available. Kopp[260] as early as 1855 called attention to instances of sudden death in childhood following cyanosis and dyspnea in which at necropsy nothing abnormal was found except a large thymus, but Paltauf's article was important because he recognized that something besides a mechanical factor of possibly increased pressure on the respiratory passages must be responsible in many instances.

Certain phenomena are now usually considered as being parts of the clinical and pathologic pictures of status thymicolymphaticus. Haven Emerson[261] has presented in his article a summary of the clinical findings in adults, of which some of the most striking refer to the secondary sexual characteristics. For example: Males frequently show a feminine configuration, with feebly developed beards and a feminine distribution of pubic hair; and females frequently show correspondingly masculine characteristics. In children the sexual characteristics of the condition naturally are not so prominent, but, as in the

case of adults, a general hyperplasia of lymphatic tissues may be made out, and a definitely enlarged thymus may be recognized by percussion and by the *x*-ray. It is not unusual in these cases for the thymus to be enlarged to 10 times its normal size, and it may be nearly as large as the heart or as a lung. A lymphocytosis usually occurs, and there is said to be a hypoplasia of the chromaffin system (Wiesel).[262] In adults the thyroid is usually enlarged but not so commonly in children. The child may die suddenly with a severe attack of dyspnea or even without any marked evidence of dyspnea. In other cases several attacks of severe dyspnea with stridor and cyanosis may occur.

Treatment.—The clinical picture suggests a mechanical dyspnea so strongly that it would seem that a partial thymectomy should be more commonly performed as a life-saving measure during the acute attack, since even in fatal cases there is often a period of from 20 minutes to one-half hour from the onset of the attack before death. Tracheotomy is of no avail because the tracheal tube often does not reach the trouble. Children who have survived an attack or two of severe dyspnea and who present evidence of an enlarged thymus should perhaps be given *x*-ray therapy over the thymus region in order to reduce its size. It is quite possible, however, that experience will show that extensive fibrosis may occur as a result and that the residual scar tissue itself may cause effects similar to those of pressure. An important prophylactic measure is to avoid all surgical procedures, except those which are urgently required, in children in whom there is any suspicion of status lymphaticus.

The association of exophthalmic goiter with enlarged thymus will not be discussed here because of the rarity of the former condition in children.

Inflammations of the thymus, such as abscess, are extremely rare and need only to be mentioned. Tuberculosis of the thymus is of no surgical interest because it is always part of a generalized process.

SURGICAL DISEASES OF THE PERICARDIUM

The principal affections of the pericardium which are of surgical interest are those which result from a suppurative inflammation. Foreign bodies occasionally have to be removed but these are so rare in children that they require no special comment. The technique of their removal involves a pericardiotomy which will be described anyway in the treatment of pericarditis.

Suppurative pericarditis is not uncommon in children. It is usually secondary to an acute inflammation of some other organ in the chest; most commonly it occurs in conjunction with pneumonia and especially when the pneumonia is complicated by empyema. In the epidemic of streptococcal bronchopneumonia in the army camps the incidence of suppurative pericarditis was very high. In 100 necropsies performed on patients with empyema at Fort Riley upon whom no operation had been performed, pericarditis (either serofibrinous or purulent) was found by Stone[47] in 46 cases. Since even in the sero-

fibrinous cases the fluid contained large numbers of hemolytic streptococci it is fair to assume that the majority of these cases would have become suppurative if the patients had lived long enough. This assumption conforms to what was well known concerning the transformation of serofibrinous pleural exudates into purulent ones. The incidence found by Stone, however, is higher than that which usually obtains in civil life in ordinary series of pneumonia. Nevertheless the fact that suppurative pericarditis is nearly always a complication of some other very severe condition explains to a considerable extent the grave prognosis which it carries. It is sometimes a complication of pyemia, especially of a pyemia which has had its origin in an osteomyelitis.

The frequent association of suppurative pericarditis with empyema may be easily explained on the basis of a direct extension from the pleura through the pericardium. In experiments on dogs performed in 1918, the writer with R. D. Bell[45] showed that when an empyema is produced by direct injection of very virulent hemolytic streptococci into a pleural cavity a pericarditis and even an empyema of the other side commonly results. As indicating the direct extension of the infection it is interesting that, under the conditions of the experiment, the number of organisms is less in the exudate of the pericardium than in the injected pleural cavity and those in the other pleural cavity are still less than those in the pericardium. If the animal lives for four or five days, a marked difference in the appearance of the exudate in the different places is discernible. The pericardial fluid, for example, is less purulent than that in the injected pleural cavity, but it is more purulent than that in the other pleural cavity.

The pathology, symptoms and diagnosis of pericarditis have been fully discussed elsewhere, and for that reason emphasis will be placed only on the surgical treatment. By surgical treatment here is meant incision and drainage. A preliminary aspiration of the pericardium should always be undertaken before a pericardiotomy is performed, in order to be sure of the presence of pus. Usually there is no great difficulty in finding it with a needle if pus is present, since in the majority of such cases the pericardium is enormously distended. The chief dangers of paracentesis are contamination of the pleura with a resultant empyema, injury to the internal mammary artery, and puncture of the heart itself. Several points of election have been designated as indicating where the needle should be introduced. These are shown in Fig. 47. In order to avoid the internal mammary vessels the needle should be inserted either close to the left border of the sternum or about 2 cm. from its border. If due care is exercised the chance of doing harm seems slight. The needle should be inserted slowly and contact with the heart is often recognized by feeling its beating. If that occurs the needle should of course be withdrawn slightly.

The possibility of opening the pericardium with an incision for drainage was suggested as long ago as 1653 by Riolanus[263] but appar-

ently such an operation was first performed by Desault[264] in 1798 through an incision between the sixth and seventh ribs. In modern times the necessity of establishing drainage in this condition has been

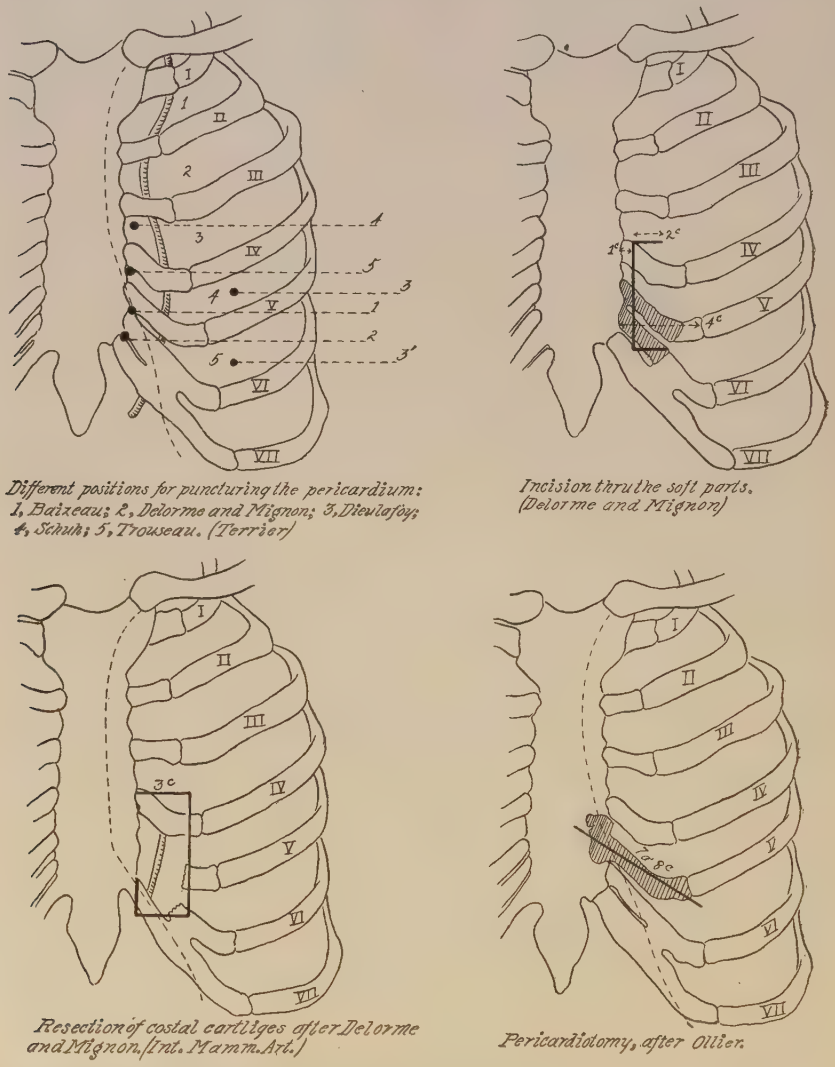
Different positions for puncturing the pericardium: 1, Baizeau; 2, Delorme and Mignon; 3, Dieulafoy; 4, Schuh; 5, Trouseau. (Terrier)
Incision thru the soft parts. (Delorme and Mignon)
Resection of costal cartilges after Delorme and Mignon. (Int. Mamm. Art.)
Pericardiotomy, after Ollier.

FIG. 47.—Diagram showing various incisions for pericardiotomy and for paracentesis of the pericardium.

generally recognized. Indeed there can hardly be any argument against the logic of removing the accumulated exudate and providing for drainage, for not only is it dangerous from the standpoint of its septic qualities, but also the mere presence of the large amount of

fluid in the pericardium acts mechanically to embarrass the action of the heart. The question then arises merely as to the best way of accomplishing this. As in the case of suppurative pleurisy, the same argument arose concerning aspiration and incision. In a very extensive article with an exhaustive bibliography Venus[265] collected all the cases in the literature reported up to 1908 which had been treated by one of three methods, simple aspiration, pericardiostomy through an intercostal incision and pericardiostomy after rib resection. From his article I have collected the cases in children under 15 years of age. Altogether there were 52 such cases reported. Of this number, 19 were treated only by aspiration, usually repeated, and 13, or 69 per cent., died. In 18 cases a pericardial opening was made through an intercostal incision; of this number 10, or 56 per cent., died. In another series of 15 cases a pericardial opening combined with rib resection was made; of this number 10, or 66 per cent., died. If one were to rely on statistics it would seem from the foregoing that the operation which gives the best drainage gives little, if any, better results than the one which gives the poorest drainage. But, as is well known, too much confidence cannot be placed in statistics, especially when they concern a relatively small number of cases. As a matter of fact, when one estimates the mortality in all the 197 cases collected by Venus (including adults as well as children), he finds only 31 per cent. listed as cured with aspiration, 44 per cent. after intercostal incision and 55 per cent. after pericardiostomy combined with rib resection. Once again, however, it must be understood that too much reliance cannot be placed on these statistics, because of the tendency to report only successful cases. Suppurative pericarditis is a much more common condition than the cases collected by Venus would seem to indicate, and one is tempted to conclude that when due allowance is made for the relatively greater numbers of successful cases reported, the actual percentage of successes is probably very much less than it seems to be. The condition will always be accompanied by a very high mortality because it usually represents merely one aspect of a very severe infection, as pneumonia, pyemia from osteomyelitis, etc.

In a recent article (1921), Pool[266] has added another successful case of his own in a child on whom he operated by a pericardiostomy combined with resection of the sixth and seventh costal cartilages. He has also compiled the cases in the literature since the article by Venus, and he finds that a total of 99 cases have been reported in which pericardiostomy has been employed. Of these there were 53 recoveries and 46 deaths. His compilation includes those of Roberts[267] in 1897; Porter,[268] 1900; Venus,[265] 1908; Eliot,[269] 1909; and Rhodes,[270] 1915.

Several methods have been proposed by which to gain access to the pericardium for drainage. These consist in general of:

1. Those which traverse the thoracic wall.

2. Those which approach the pericardium from below the costal arch.

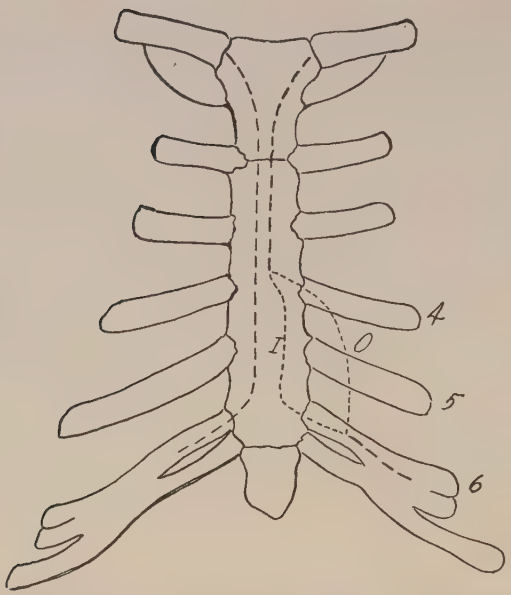

FIG. 48.—Reflection of pleura. On left side anterior limits of pleura may lie anywhere between the dotted lines. Outer position (*O*) is most frequent; inner (*I*) least frequent. (After Pool.)

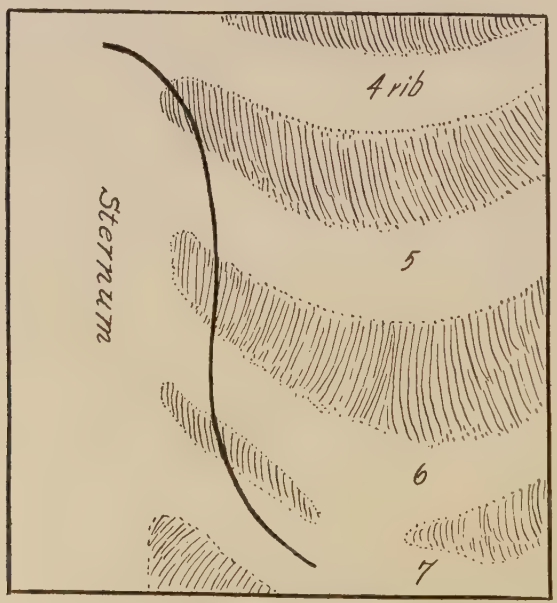

FIG. 49.—Incision for pericardiotomy. (After Pool.)

Various procedures have been recommended for reaching the pericardium through the thoracic wall. Desault advised an intercostal incision between the sixth and seventh left ribs and an incision of about 0.5 cm. into the pericardium. Romero's[271] and Parker's[272] methods were similar. Methods based on the principle, however, of a simple intercostal incision have been rather generally abandoned. They give insufficient exposure and subject to great danger the internal mammary vessels and the pleura. In order to give satisfactory exposure and adequate drainage one or more of the costal cartilages must be resected.

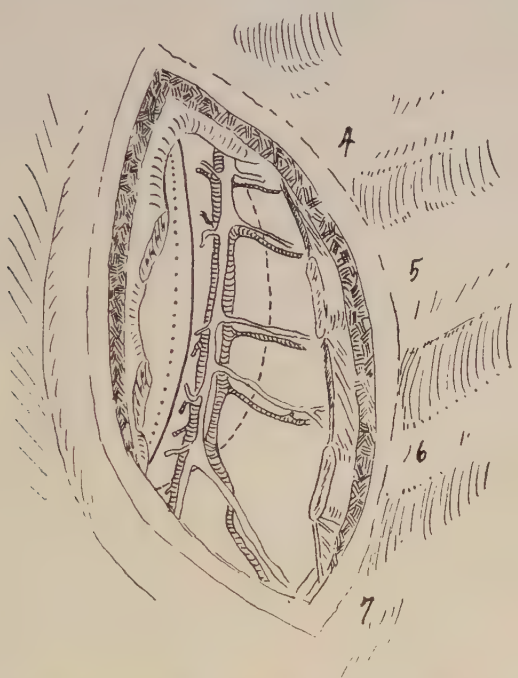

FIG. 50.—Portions of fifth, sixth and seventh cartilages removed. Approximate relations of lung, pleura and mammary vessels to line of incision in pericardium. Line of dashes, lung; continuous line, pleura; dotted line, line of pericardial incision. (Diagrammatic after Pool.)

Ollier[273] recommended the resection of the fifth left costal cartilage through an incision parallel to it. Kocher[274] and Axhausen[275] have each advised the resection of the sixth costal cartilage. The procedure of Delorme and Mignon[276] involves the resection of both the fifth and sixth left costal cartilages and a vertical incision of the pericardium. It has the advantage of giving good drainage and of minimizing the danger of injury of the pleura. A brief description of this operation is as follows:

At about 1 cm. outside of the left border of the sternum a little above the lower border of the seventh costal cartilage, a vertical incision is begun which stops at the level of the upper border of the fourth

cartilage. From the extremities of this incision two transverse cuts are made of about 2 cm. each, extending to the left. The soft parts are then dissected from the cartilages and ribs to about 1 cm. inside the left border of the sternum and about two fingers' breadth outside of it. Section of the fifth and sixth costal cartilages at the level of their sternal insertions is performed and they are drawn outwards and fractured at a distance of about 4 cm. from the sternum. Carefully then one carries the vertical incision down through the perichondrium and the intercostal muscles until the triangularis sterni muscle is seen. With the finger the muscle is then carefully separated from the sternum, or it may be split and the anterior surface of the pericardium separated from the cellular tissue in front of it and from the pleura. The pericardium appears as a whitish structure. If it is greatly distended pulsation may not be apparent. The anterior portion is sewed to the lower portion of the wound and the pericardium is incised vertically from below upwards for a distance of 2 or 3 cm.

Resection of the sixth and seventh cartilages and a portion of the left border of the sternum has been recommended by Voinitsch-Sjanoshenski[277] and by Rehn;[278] and resection of the seventh cartilage by Mintz.[279] Pool considers that, in order to secure satisfactory drainage, it is essential that the seventh cartilage be resected, and, in order to avoid injury to the pleura, a vertical incision should be made in the pericardium. He recommends the removal of portions of the fifth, sixth and seventh cartilages, and states that by this means an incision approximately 2 in. long can be made in the pericardium of the adult. Accordingly he has devised an incision and an operation, the description of which is quoted:

"The incision begins at the middle of the sternum at the level of the lower margin of the fourth costal cartilage; curving, it passes downwards and to the left to the upper margin of the chondrosternal junction of the fifth; then downwards close to the left edge of the sternum, crossing the fifth and sixth cartilages to the middle of the seventh cartilage; curving outwards it follows the seventh cartilage. The soft parts are freed and retracted, the resulting wound being an ellipse. The seventh costal cartilage is divided at the sternum. The soft parts are detached along its borders and the cartilage is lifted. It is easily freed from the perichondrium posteriorly. A complete subchondral resection is not attempted because the perichondrium anteriorly and at the borders is firmly adherent and is separated with difficulty. The cartilage is fractured about 2 in. from its sternal end and removed. The same procedure is carried out with the sixth and fifth cartilages. The thin layer, including internal intercostal muscles and posterior perichondrium, is incised vertically and easily separated from the underlying tissues. This exposes the internal mammary vessels. At the upper part of the wound they lie about ½ in. from the sternum. They should be ligated above and below to lessen the danger of secondary hemorrhage. The thin triangularis sterni is separated from the sternum, and with the finger or blunt instrument the under-

lying fat, and with it the edge of the pleura, is displaced outward. The pericardium is thus exposed and is opened between forceps, about 1 cm. from the edge of the sternum. The incision should extend downwards to the reflection of the pericardium to the diaphragm. While the incision is in general vertical, it is advisable that it be slightly curved with the concavity towards the sternum. This allows a better separation of the edges and favors drainage. If possible the edges of the pericardium should be sutured to the skin or superficial soft parts to diminish the danger of mediastinitis."

A consideration of the method of maintaining drainage is important. In order to minimize a disturbance of the heart, it is obvious that a rigid drain should not be kept in contact with the heart. If a tube is employed it should be well protected with gauze and should not project far into the pericardial cavity. A cigarette drain is probably preferable. A partial sitting posture is of considerable advantage in facilitating drainage, as this position tends to prevent the accumulation of pus deep in the posterior portions of the pericardium. The drain should be removed early. Pool recommends its removal in 36 hours.

As was the case in the development of the treatment of empyema, so also in pericarditis, the question of irrigation of the pericardium has been a subject of considerable controversy. Bronner[280] and von Eiselsberg[281] have been advocates of irrigation. In Parker's[282] case the patient died suddenly on the operating table during an irrigation. Souligoux thinks irrigation should be omitted. Pool thinks irrigation with Dakin's solution should be used. In two cases in which the writer had personal experience in the streptococcal epidemic in the army, irrigations with Dakin's solution were carried out; and although both patients eventually died, there was no reason to think the irrigations had done harm. In both cases the pericarditis was complicated with empyema, and at necropsy both lungs were found to contain multiple small abscesses.

Several writers have reported the occurrence of marked irregularities of the heart after irritation of the pericardium. Heitler[283] found, for example, that in dogs mechanical or electrical stimulation of the pericardium induced an irregularity in the cardiac rhythm. D'Agata[284] also found in animal experiments that a sudden drop in blood pressure occurred if the pericardium were grasped or incised. Harrigan,[285] in a human case, found that a temporary arrest of the heart occurred when the pericardium was incised for suppurative pericarditis. In a small number of experimental operations on the heart in dogs I have never seen any arhythmia occur merely from grasping or incising the pericardium if the heart itself were not disturbed in the procedure. I have also failed to observe the phenomenon in operation on the human when the pericardium was involved. Further work should be done on this point. It is possible that reflex disturbances of a serious nature may occur in some cases and not in others, as seems to be the case in the pleural reflexes which have been extensively studied by Capps and Lewis.[71]

The ultimate functional results of pericardiotomy for acute suppurative pericarditis are rather variable; but there is no apparent reason for ascribing the poor results to the operation, since it is well known that serious effects of adhesions in the pericardium frequently follow cases of suppurative pericarditis in which no operation has been performed. It is probable that early drainage would result in fewer poor functional results. Lilienthal's[286] patient was well 20 years after the operation; Walzel's[287] nine years later; Kiliani's[288] seven years. Eliot's[289] two years; Peters'[290] 11 months; Pool's eight months. On the other hand, Davis'[291] patient, an 11 year old boy, showed marked adhesive pericarditis one year after operation; and Le Conte's[292] patient, a man aged 36 years, was unable to return to work four months after operation because of persistent papitation.

Late Results of Suppurative Pericarditis—Chronic Mediastinopericarditis.—As might be expected, a suppurative process involving the pericardium frequently results in the formation of adhesions which seriously interfere with the normal work of the heart. Adhesions are found in various locations. They may be between the parietal and visceral surfaces of the pericardium, thus leading to an obliteration of the pericardial cavity; and they may also involve neighboring organs and structures. It is common for the heart to become adherent to the anterior chest wall (the sternum, the ribs and the costal cartilages). The lungs and the diaphragm also may become involved in these adhesions. Even calcification of the pericardium may occur, as has been reported by Diemar[293] and by Wells.[294] The significance of these adhesions is that the work of the heart is seriously impaired, particularly in those cases in which firm adhesions to the chest wall exist, for under such conditions the heart, at each systole, is compelled to pull against rigid structures.

Pick[295] in 1896 called attention to a pseudocirrhosis of the liver which not infrequently occurs in connection with an adhesive pericarditis. Clinically, these cases showed ascites, hepatic enlargement, slight jaundice, general weakness and dyspnea. There was occasionally an enlargement of the superficial abdominal veins and edema of the feet but not any special cardiac features. The livers at necropsy presented features of both an interlobular cirrhosis and perihepatitis; a chronic perisplenitis was present and the peritoneum was thickened. Rolleston[296] has given a good description of the pathology of the condition.

Patients with adherent pericardium commonly show a filling of the cervical veins during inspiration and a *pulsus paradoxus*, both of which signs were originally described by Kussmaul[297] in 1873. Visible retraction of the posterior tenth and eleventh intercostal spaces, a sign first described by W. Broadbent,[298] is usually present; and visible systolic retraction of the costal cartilages and the lower end of the sternum may be present according to J. H. Broadbent.[299] Ellsworth Smith[300] has called attention particularly to the diagnostic value of a systolic tugging upwards of the diaphragm as seen with the fluoroscope. Also

according to Smith, the first *x*-ray demonstration of pericardial adhesions was made by Benedikt[301] in 1897. At the present time the *x*-ray is of the greatest value in establishing the diagnosis, since often the exact location of the adhesions can be recognized with precision by this means.

The treatment of pericardial adhesions obviously must be based on a plan which will give mechanical relief. The essential indication is to change the conditions in such a way that it will no longer be necessary for the heart to pull against the rigid chest wall with each systole. This indication can be met only by surgical interference. To Brauer[302] belongs the credit for having first devised and carried out an operation which has now been performed in a sufficiently large number of cases to have established it as the most satisfactory method of treatment of this condition as yet devised. Brauer named the operation cardiolysis. It consists in the resection of the fourth, fifth and sixth ribs and costal cartilages over the heart. The operation can usually be performed in a satisfactory manner with local anesthesia. The skin incision constitutes three sides of a rectangle over the heart, so that a flap of skin and muscle is turned back from the underlying ribs. The base, or pedicle, of the flap is in the axillary line, and the free edge at the sternal margin. After turning up the soft parts the fourth, fifth and sixth ribs are resected subperiosteally from a point slightly outside the nipple line to the sternum. The respective costal cartilages are also removed, but the sternum is left intact. The periosteum and perichondrium are removed insofar as it can be done without seriously running the risk of opening the pleura. It is not necessary to remove all of the periosteum. The skin and muscle flap is then replaced and sutured. Delagénière[303] has recommended a much more extensive removal of the thoracic wall.

The first to perform the operation in this country was J. E. Summers[304] of Omaha in 1913. In his article Smith reviews the literature extensively and summarizes the results. He reports a strikingly successful case of his own operated on by Mudd. In his summary of results he finds that a favorable result was obtained in 24 cases and a failure in nine cases. The average period of relief from symptoms was about 17 months. In several instances patients who had been bedridden were enabled to resume their normal occupations. In view of the inefficacy of any other form of treatment it would seem that this operation should certainly be done more often.

DIAPHRAGMATIC HERNIA

Cooper[305] in his classic work on hernia published in 1804 was one of the first to describe diaphragmatic hernia. He recognized two main varieties, congenital and acquired. Of the congenital hernias some have true peritoneal sacs and others have none. The acquired hernias have no peritoneal sacs. They should more properly be regarded as eventrations rather than as hernias. The congenital hernias without sacs are of little clinical importance because the infants

with this condition usually die soon after birth. The true hernias and even some of the eventrations occur through the normal foramina of the diaphragm, as, for example, through the foramen for the aorta, the esophagus, etc. Most of the acquired eventrations, however, occur as a result of an injury and may therefore involve any part of the diaphragm. The protection offered by the liver to the diaphragm diminishes the possibility of the occurrence of an eventration on the right side so that except in the case of congenital hernias, it is rare to find a diaphragmatic hernia on that side. The acquired type may follow any kind of an injury, as for example, one in which there has been a severe crushing of the abdomen or thorax, but most commonly it is a result of a penetrating injury, such as a stab or gunshot wound. Heyd[306] states that approximately 10 per cent. of all chest wounds in the American Army during the late war were associated with an injury to the diaphragm, and that about 12 per cent. of all abdominal wounds were combined with an injury to the chest or diaphragm. Not all of these cases, however, developed diaphragmatic hernias. The most exhaustive article published on diaphragmatic hernia was by Salomoni[307] in 1910 with an analysis of 1000 cases.

The pathology of the condition is extremely varied since the associated injury usually present is also varied. The organ which is most commonly appearing in the hernia is the stomach but frequently intestine is also present.

The symptoms are usually suggestive of intestinal obstruction, although often no symptoms are present, and cases have been described in which a congenital type of hernia has been discovered at necropsy upon adults who have led fairly normal lives. Frequent vomiting and borborygmi are commonly complained of. The diagnosis is easy with the *x*-ray, but before its discovery comparatively few cases were recognized during life. It is important to remember that a patient with a high diaphragm on the left side may give physical signs somewhat like a diaphragmatic hernia, such as a tympanitic percussion note, distant breath sounds, gurgling, etc. An *x*-ray examination, however, with a barium meal will certainly reveal the presence of stomach or intestine in the thorax. Giffin[308] has thoroughly discussed the diagnosis. The *x*-ray diagnosis has been particularly elaborated in the article by Becker;[309] and Königer[310] has dwelt especially upon the differential diagnosis between hernia and a high diaphragm because of atrophy.

The treatment is of course surgical. Scudder[311] in 1912 was able to find in the literature records of 53 cases in which operation was performed for diaphragmatic hernia. In 11 cases the approach was through the thorax with a result of seven recoveries and four deaths. In 42 cases the approach was made by a laparotomy incision with the result that only seven recovered and 35 died. Scudder himself reports an additional successful case operated on by the abdominal route. Bevan[312] has recently reported three cases operated on successfully by himself through the abdominal route. Riggs[313] has also recently

reported a case successfully handled by laparotomy. Frank[314] in a case of supposedly congenital hernia attempted operation by the abdominal route but was compelled later to resort to thoracotomy. Breitner[315] has just published from Eiselsberg's clinic a comprehensive article in which he has tabulated the names of those surgeons who prefer the abdominal and thoracic approach respectively. There is about an equal division. After reaching the site of the hernia various measures have been used to assist in the closure of the opening. For example: The stomach on several occasions has been sutured to the diaphragm to reinforce the closure. Even the spleen has been used for the same purpose. Downes[316] in a congenital case found it impossible to reduce the hernia and made a gastro-enterostomy by which the symptoms were relieved.

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CHAPTER LXVII

MEDIASTINAL TUMORS

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Mediastinal tumors in childhood are exceedingly rare. In 1889 Hare[1] collected the literature on mediastinal disease. Among his cases were both primary and secondary cases of involvement of the mediastinum. In his 134 cases of carcinoma, five were in children, ages from 4 to 12 years. In his 98 cases of sarcoma, nine were in children of from 5 to 14 years. Of this nine the case of Hutton is given twice so that there really remains a total of eight cases of sarcoma in children, among 97 cases in all ages. Of his 21 cases of lymphoma and lymphadenoma only one was in a child and that was in a boy six years old. No case of fibroma or echinococcus cyst was recorded in children.

Morris[2] in 1905 collected 67 cases of dermoid cyst of the mediastinum. Of these five were in children. One of these was noted to have undergone sarcomatous change.

Steffen[3] in his collection of malignant tumors in children reports only three occurring in the mediastinum, all of thich were lymphosarcomas.

Edwards[4] supplemented the list of Hare, giving one more case of carcinoma, one more of sarcoma, and repeating the case of lymphoma. The youngest case in these groups is three years, the majority of cases occurring between 8 and 12 years. The records here are taken for children of 14 years or under.

The most common tumors to be found in the mediastinum of children are the lymphosarcomas and dermoid cysts. Carcinomas are almost always secondary, and lymphomas, fibromas and echinococcus cysts must be extremely rare in children. Schmincke[5] has reported a case of congenital lymphangioma of the anterior mediastinum and Foot[6] has recently noted a case of malignant thymoma in a boy 9 years old.

Carcinoma.—As just mentioned carcinoma is practically always secondary. The general symptomatology does not differ materially from that of lymphosarcoma except that is is often possible to find the primary seat of the disease.

Sarcoma.—The sarcomas found in the mediastinum of children are nearly always of the lymphosarcoma type. They may have their origin from the thymus or from the peribronchial lymphatic glands as in the cases reported by Guidi.[7]

de Lange and van Goor report[8] a case of Lymphosarcoma of the mediastinum in an infant which died at 8 weeks of age (congenital) and showed metastases in the liver and Money[9] has reported a sarcoma of the posterior mediastinum in an infant 15 months old. This was a round-cell sarcoma without any striated muscle tissue.

Sarcomas, too may have their origin in a dermoid cyst as in the case reported by von Eiselsberg[10] in a child three years old, and the case of Halle and Salin[11] in a child 13 years old. The symptoms of lymphosarcomas of the mediastinum do not differ materially from the symptoms of enlargement of the lymphatic glands as seen in Hodgkin's disease. The symptoms are nearly always those of pressure. In the early stages of the disease there is found a brassy cough, spasmodic in character, not materially different from the cough of whooping cough except that there is no crow. The cough is no different from that produced by the massive enlargement of the peribronchial glands in tuberculosis and is not characteristic. Accompanying this there is a certain amount of malaise, perhaps some headache, loss of appetite, but there seems to be little in the way of pressure pains. Occasionally laryngeal stridor is noted due to spasm of the glottis and irritation.

Dyspnea is noted early and gradually becomes more marked. These tumors are frequently accompanied by pleurisy with effusion which may to an extent account for the dyspnea, but dyspnea grows progressively with the increase of the neoplasm. It is increased when the patient is lying flat. Pressure on the blood-vessels may cause distention of the vessels of the neck and thorax. On examination of the chest there is very frequently to be found signs of a pleural effusion which may occur on either side. However, further examination will reveal greater width of dulness at the base of the heart and increased dulness down the spine with perhaps a widened dulness between the scapulæ. The breast muscles may or may not be very much affected.

Involvement of the pleura by the tumor is certainly a rarity, but if present, puncture of the pleura may show a bloody fluid. *X*-ray examination shows a broadening of the shadow above the heart which may become very marked and at times may have rather an irregular outline. Examination of the blood and urine shows nothing characteristic. Frequently a simple anemia is present.

Course.—As the disease advances there may be present a low irregular temperature. All symptoms become worse and the child dies either from exhaustion or from respiratory failure.

Diagnosis.—It is very difficult to differentiate tumors of the mediastinum from other masses in that region. Enlargement of the thymus shows by no means the same tendency to rapid increase in size nor is there the same degree of pressure. The general condition of the child is as a rule not very much affected. Enlargement of the peribronchial glands due to tuberculosis may cause some difficulty especially in the early stages. Most cases of lymphosarcoma of the mediastinal glands have been first diagnosed as tuberculosis but the rapid growth of the

sarcoma mass, especially if the tuberculin tests are negative, helps in the course of time to distinguish between the two conditions. Hodgkin's disease may have as rapid a development as does lymphosarcoma, but it is usual to find masses of glands in other parts of the body, especially in the neck and axilla, which will help us in differentiating the two conditions.

The only other tumor of the mediastinum which is present in sufficient frequency to cause much difficulty in diagnosis is the dermoid cyst (see below).

Treatment.—The recent report of Burnam[12] leads us to hope for some benefit in these cases from the use of radium.

Dermoid Cysts.—The dermoid cyst begins most often in the anterior mediastinum. It varies in size from that of a walnut to a child's head. It is usually found beneath the upper half of the sternum always either to one side or the other. It is frequently found in the pleural sac and always adherent to the surface of the structure. The cyst wall is variable as to its thickness and may have undergone a sarcomatous change. The contents vary greatly, some consisting only of hair and skin elements, others resembling a true teratoma in structure. Not infrequently the contents become infected giving rise to symptoms of a septic nature.

The dermoid cysts do not vary materially from lymphosarcomas in their symptoms and physical signs. They may remain latent for years and suddenly increase. At times this increase in size is due to infection of the cyst contents. Pain seems to be a more prominent symptom than in lymphosarcoma and pleural effusion is found here as in the other condition. The *x*-ray shows nothing characteristic. Occasionally the contents may rupture into the bronchus and the material be coughed up. When the characteristic contents of the dermoid cyst are brought up in this manner, the diagnosis is comparatively easy. More frequently, however, after infection it points externally. The point of evacuation of the pus is variable but a rather frequent location is anterior just below the left clavicle.

The growth of the dermoid cyst may be extremely slow. Very frequently, however, after remaining latent for many years there is a marked and sudden increase in size. This increase in size is much more rapid than is seen in cases of lymphosarcoma and much more marked, as a rule, than is to be found in other masses of the mediastinum such as enlargement of the thymus and peribronchial glands, either from tuberculosis or Hodgkin's disease. If the diagnosis is made this condition offers some hope from operation, which, of course, consists in removal of the tumor. This has been successfully done even in children.

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CHAPTER LXVIII

PHYSIOLOGY OF CIRCULATION

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The Prenatal Circulation.—Owing to the difficulties attendant upon an experimental study of the prenatal circulation and the limitations of its direct clinical study, our physiological conceptions of the circulation before birth are largely based upon inferences drawn from anatomical studies. While this method of obtaining information has in general been tempered by the conscientious application of the known laws of physics and general physiology, it allows the use of so much individual discretion—not to say imagination—in their application that many of our current views regarding the dynamics of the prenatal circulation must be regarded as probable and tentative rather than as demonstrated and quite final.

Anatomical studies indicate that the route taken by the blood around the body of the fetus differs essentially from that followed after birth. The pathway taken by the blood from the placenta to the right heart is clearly established. Blood relieved of carbon dioxide and waste products in the placenta and replenished with oxygen and nutritive constituents is returned to the fetus by the umbilical vein which discharges by far its larger volume directly into the inferior vena cava but contributes through a branch, the ductus venosus, a smaller volume to the liver circulation. In the inferior vena cava, the placental blood mingles with the venous blood returning from the lower portions of the body so that a blood partly placental and partly venous is returned to the right auricle by the inferior vena cava. Physiologically, the quality of this mixed blood may be said to be superior to that simultaneously entering the auricle from the superior vena cava and coronary veins. Do these streams entering the right auricle intermingle and mix so that one quality of blood leaves the right auricle, or is there a mechanism which provides that the blood of the better quality entering the auricle from the inferior vena cava is directed into the left auricle? According to the theory of Haller-Sabatier (1779–1791), which is generally followed in text-books, the latter is the case. This theory has been interpreted in two ways: Either that the foramen ovale is the real outlet of the inferior vena cava so that all or practically all of the blood from the inferior vena cava passes to the left auricle; or, as more commonly interpreted in text-book diagrams, that the streams from the superior and inferior vena cava cross in the right

auricle without mixing. Such a separation of the streams is credited to the fact that the Eustachian valve directs the stream from the inferior vena cava toward the foramen ovale. "A critical examination of this theory," says Pohlman,[55] "shows it to be physically impossible, morphologically inaccurate and developmentally unnecessary." It is simple to show by physical principles that it is impossible to prevent the mixture of two blood streams entering the auricle during its relaxation, and equally simple to prove by dynamic laws that the blood leaves the inferior vena cava under a pressure so small that it could in no conceivable manner shoot a stream across the auricle to the foramen ovale. Unless some other, as yet undiscovered, physical mechanism can be shown to exist, we must conclude

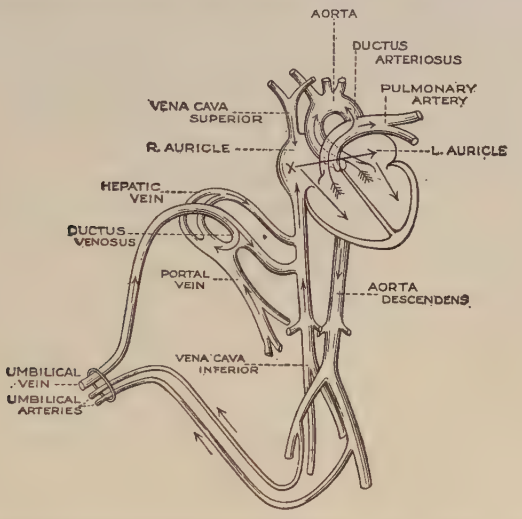

FIG. 51.—Schematic figure showing the course of the prenatal blood stream.

upon physical grounds alone that the possibility that the streams from the superior and inferior venæ cavæ are in any way separated is very improbable. This conclusion receives direct experimental support from the work of Pohlman[55] who found that corn-starch granules injected into the inferior vena cava via the umbilical vein of living pig embryos could be recovered in equal numbers from the blood of the left and right ventricles; whereas, we should not expect to find them in the right ventricle if a mixture of blood in the right auricle had not occurred. Similarly, starch granules injected by the superior vena cava appeared in equal numbers in the right and left ventricles.

We must conclude, therefore, that while the subject is still open for much further experimental work, all the present physiological considerations supply no evidence that the currents from the superior and inferior venæ cavæ are kept separate, but strongly favor the view that a thorough mixing of blood takes place in the right auricle.

Starting from these premises, the further mechanism of the fetal circulation will be considered (Fig. 51). During auricular relaxa-

tion, a difference of pressure is created between the cavities of the two auricles on the one side and the venæ cavæ on the other. This difference is responsible for the inflow of blood which fills, first, the right auricle from the veins and then the left auricle through the foramen ovale. During ventricular diastole a similar difference of pressure between the cavities of the ventricles and auricles is rapidly created which is responsible for the filling of the ventricles. During auricular systole the pressure within both the left and the right auricle rises. This prevents the inflow of blood from the veins. It is inferred but not demonstrated that the pressure rises equally in both auricles and so prevents a transfer of fluid through the foramen ovale. As to whether or not the flap covering the foramen closes we have no information. When ventricular systole occurs blood is ejected from the left ventricle into the aorta and by the right ventricle into the pulmonary artery. Simple experiments of Pohlman[55] indicate that the pressures developed within the two ventricles are equal. As the lung vessels remain unexpanded, only a small stream of blood passes through this circuit to the left auricle, but the major portion of the volume ejected into the pulmonary artery is shunted by a communication, the ductus arteriosus, into the aortic system. We have, then, during fetal life, two ventricles acting together to pump blood into the systemic vessels (Fig. 51).

Changes in the Dynamics of the Circulation at Birth.—Birth may be said to begin with the onset of uterine contractions which serve to expel the child and separate the placenta from its uterine attachment. During every uterine contraction, the fetal heart has a tendency to become slower (Ziegenspeck).[72] The cause is not clearly established. The fact that the vagus fibers both in chick embryos (Botazzi)[56] and rabbits (Soltman)[56] are not irritable before birth indicates that the slowing is due neither to a cerebral compression during delivery nor to a periodic asphyxiation from compression of the cord. More probably each uterine contraction forces a larger volume of venous blood from the placenta into the vena cava, and this engorgement causes the slowing of the heart.

For a short interval after delivery, the child remains in functional connection with the placenta. Due to the separation of the placenta, aeration of the fetal blood soon becomes imperfect, however. The accumulation of carbon dioxide thus produced has a two-fold action: It causes a more vigorous ventricular discharge which elevates the arterial pressure; it stimulates the dormant respiratory center, causing the first inspiration and lung inflation. Both mechanisms act to open up the collapsed pulmonary vessels; the former by exerting increased pressure from within, as experiments on atelectatic lungs show; the latter by exerting a traction from without (Cloetta[9]). This increases the capacity of the pulmonary vessels and reduces the resistance to the flow of blood through the lungs. Consequently, the pulmonary vessels first fill with blood and, this accomplished, a pulmonary flow to the left auricle is established.

According to dynamic laws, this sudden filling of the pulmonary vessels would cause not only a marked reduction of pressure in the pulmonary artery, but also a backflow from the aorta through the ductus arteriosus, with a consequent sudden fall of aortic pressure. According to Strassmann,[58] such a regurgitation is prevented by the fact that the ductus arteriosus passes obliquely through the arterial wall and as soon as any difference of pressure between the two sides occurs is closed off, much like the ureter, by the valvular action of the aortic wall. Keating and Edwards[35] credit Forbes with the idea that the ductus arteriosus is closed by a traction exerted by the descent of the diaphragm upon the fibrous structures extending from the tendinous center of the diaphragm to the aortic arch. If these mechanisms are effective, there is established *at once* a difference of pressure between the aorta and the pulmonary artery for the latter is drained by vessels of very low resistance and the former confronted by the much higher resistance of the entire systemic circuit.

The sudden opening up of a capacious vascular area in the lungs which hitherto contained no blood, together with the fact that the aortic supply is suddenly derived from one ventricle instead of two, can have but one consequence, i.e., to reduce the minute volume of arterial blood and consequently the arterial pressure. We have no direct evidence that this occurs after birth, but the idea is supported by the fact that the heart accelerates immediately after birth (Ziegenspeck).[72] This is probably a compensatory mechanism tending to elevate the pressure to its former level. Within 15 minutes to one hour, conditions have so adjusted themselves that the blood pressure is maintained and the heart slows to or below its fetal rate (Ziegenspeck).[72]

The lower arterial pressure thus created soon after birth, together with the contraction of the umbilical arteries in reaction to mechanical and thermal stimuli (Bucura[5]) (Lochmann[44]) favors a smaller arterial outgo through the umbilical artery. The respiratory movements and negative intrathoracic pressure, together with uterine compression of the placenta, favors the return of venous blood to the child. For this reason, it is desirable after delivery to defer tying the cord for some time in order to allow the return of as large a quantity of blood to the child as is possible. With the establishment of the pulmonary circulation and the entrance of blood into the left auricle by the pulmonary veins, the pressure within the left auricle somewhat exceeds that in the right auricle and therefore maintains the flap covering the foramen ovale in apposition during diastole as well as in systole. By these temporary mechanisms blood ceases to flow through the ductus arterious, ductus venosus and foramen ovale and the postnatal circulation is established. The stagnant blood in these obsolete vessels first undergoes coagulation and organization, and finally contraction which serves to permanently obliterate the vessels. By this process the hypogastric arteries are entirely obliterated by the third day and the ductus arteriosus by

the thirteenth day. The foramen ovale gradually contracts in size and the valvular curtains gradually form adhesions. Weeks and months may pass, however, before complete anatomical closure replaces that first affected by dynamic changes and according to McMurrich,[45] the foramen never closes anatomically in from 25 to 30 per cent. of individuals.

The Physiology of the Heart Beat.—The four cardiac chambers contract in an orderly sequence referred to as the *cardiac cycle*. First, the auricles contract for an interval of approximately 0.1 second. About 0.024 second after their relaxation has begun the ventricles contract simultaneously. This lasts about 0.3 second and then they relax. We may thus speak of the systole and diastole of the auricles and of the ventricles, respectively; but if the contraction of the ventricles is taken as a time standard of the heart cycle, the contraction of the auricles may be referred to as the presystole of the heart.

During the early stages of embryonic development, this orderly contraction is mediated in a very simple manner. When the primitive cardiac tube is first formed it consists of undifferentiated mesoblastic cells. By the second week of development these cells begin to change their shape and propel the newly formed blood into the arteries. *Contractility*, as the property by which the cells alter their contour is called, has been acquired; and, as the cells originate their own impulses, *rhythmicity* has developed. *Irritability*, or the power to respond to stimuli, and *conductivity*, or the power to transmit impulses, are also established. Not only do the as yet undifferentiated cells possess all the fundamental functions characteristic of fully developed heart tissue, but a certain regional specialization in function is also foreshadowed. The venous end initiates the impulse and contracts first, then passes the impulse on toward the arterial end of the heart by direct cellular conduction. As the arterial end is required to advance the blood through the greater resistance of the systemic circuit, it soon develops the power of contractility to a predominant degree.

This simple arrangement for maintaining an orderly sequence of contraction, which adapts the more venous end primarily to the rôle of pacemaker and the more arterial portion to the requirements of a force pump, becomes transformed into a more intricate, specialized mechanism during the course of development. As the early mesoblastic cells gradually develop into the cardiac syncitium, the separate functions are gradually taken over by different systems of cardiac muscle with specific morphological characteristics. The ventricular cells are the first to acquire the characteristics usually associated with cardiac muscular tissue. The ends of the mesoblastic cells fuse, their boundaries merge, and longitudinal fibrillæ, the specialized contractile elements, develop throughout the length of the fibers. These characteristics give the cardiac muscle the appearance of a non-cellular structure, to which the term *heart syncitium* is applied. The ventricles are soon largely composed of a thick mass of this tissue and a similar thinner layer forms the bulk of the auricles.

While these changes are going on, the sinus venosus, as the trunk of merging veins where impulses are initiated is termed, becomes adherent to the posterior auricular wall and later is absorbed into its structure. By the invasion of connective tissue, the sinus tissue is encroached upon more and more, until at birth only a small club-shaped remnant of tissue known as the *sinus node* (Keith and Flack[36]) remains in the posterior auricular wall (Fig. 52). The fibers composing this structure differ from the rest of the auricular tissue in that they are paler in color, more fusiform in shape and contain fewer fibrils.

From the sinus node impulses are conducted radially to all portions of the auricle so that each fractionate portion is stimulated in succes-

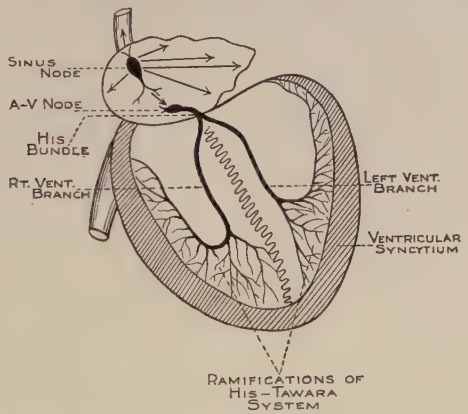

FIG. 52.—Schematic figure showing the relations of the sinus node and His-Tawara system to the auricular and ventricular syncitium, the spread of the excitation wave being indicated by arrows.

sion by the impulses conducted through its own fibers (Fig. 52). Up to the sixth or eighth week of fetal life, impulses are also conducted directly to the ventricles by the continuous contractile tissue of the auricular canal. As the valves develop, a circular, wedge-shaped ring of connective tissue gradually grows into the auricular-ventricular ring and eventually separates the auricular and ventricular musculature completely. Impulses can then no longer be conducted directly from auricle to ventricle. A new system, the His-Tawara system (*Cf.* Tandler,[59] Marceau[48]) for the conduction of impulses to the ventricle then develops. In the fully developed heart, this system may be said to begin as a node of tissue embedded in the auricular wall and spoken of as the *auriculoventricul arnode or the a-v node* (Fig. 52). It gives rise below to a thin strand of tissue which passes sub-endocardially across the auriculo-ventricular septum beneath the median tricuspid cusp forming the bundle described by His, Junior[28] and bearing his name. It curves downward and forward and, after reaching the membrano-muscular junction of the inter-ventricular septum, it divides into two branches, one going to the left, the other to the right ventricle. Each branch divides and redivides into many smaller ramifying branches

which communicate with the innermost contractile syncitium of the ventricles (Fig. 52). The cells composing this conducting system resemble more closely those of the sinus region than those of the contractile syncitium of the ventricles. They are rich in glycogen content and only faintly striated. They branch and interlace freely and are more delicate in their appearance.

When the impulses have spread from the sinus node through the auricular musculature they reach the auriculoventricular node. Here the impulse is delayed for a short interval and then propagated at the rate of from 3000 to 5000 mm. per second to the ventricular muscle. This rapid conduction insures that all portions of the ventricle are excited practically simultaneously causing every portion of the ventricle to contract at the same time.

To summarize: The sinus node becomes the rhythmic area, the His-Tawara system the conducting medium to the ventricles, and the ventricular syncitium, the chief contractile or pumping mechanism of the fully developed heart. The auricular tissue retains its original property of conductivity and specializes to only a minor degree in the function of contractility.

Clinical Methods of Studying the Fundamental Cardiac Functions. Clinically, it is important to know whether the cardiac functions proceed in a normal or abnormal fashion. Whenever the impulse is either not regularly originated at the sinus node, or fails to spread to the auricles or ventricles in the manner described above, the normal sequence of the cardiac cycle becomes disturbed and ventricular irregularity results. To determine the nature and seat of such disturbances, two procedures are made use of: the study of the venous clavicular pulse and the electrocardiogram. To understand the significance of abnormal deviations, the nature of the normal venous pulse and electrocardiograms must be briefly considered.

The Normal Venous Pulse Tracings.—If a receiving cup—preferably covered with light rubber dam—is lightly placed over the jugular bulb in the right supraclavicular region and connected to a recording tambour at once sufficiently sensitive and capable of following the volume changes in the vein, a tracing of the venous pulse is obtained. Such a tracing recorded photographically from a boy 10 years of age by means of the segment capsule of Frank (*Cf.* Wiggers[66]) is reproduced in Fig. 53. The consecutive events of the cardiac cycle, as determined by recent work, are marked upon it.

It is evident at a glance that neither the onset of auricular or ventricular systole is absolutely synchronous with any wave or oscillation. This is chiefly due to a delay in the transmission of waves to the cervical region. For practical purposes, however, this delay is fairly constant so that the relations of these two events may be determined quite accurately.

A tracing of the venous pulse shows three waves of consequence. The first wave (*a*) is related to the rise and fall of pressure within the auricle. It occurs during auricular systole and may therefore be

designated as the *presystolic wave*, or *a-wave*. The second wave (*c*), synchronous with the arterial pulse in adjacent vessels, is due to an impact from these vessels. It is designated as the *systolic or c-wave*. The third wave (*v*) reaches its summit early in diastole and falls sharply when the tricuspid valves open and blood flows from auricles and veins into the right ventricle. This is the *diastolic or v-wave*. If the delay for transmission to the neck is allowed for, it is evident that the rise of the presystolic or *a*-wave indicates the onset of auricular systole. The onset of auricular relaxation, which is not indicated by any oscillation, occurs somewhere near the end of the descending limb of this wave. The onset of ventricular systole is indicated by a small vibration (I) preceding the rise of the second wave. The end of ventricular systole is similarly indicated by a vibration or two (II)

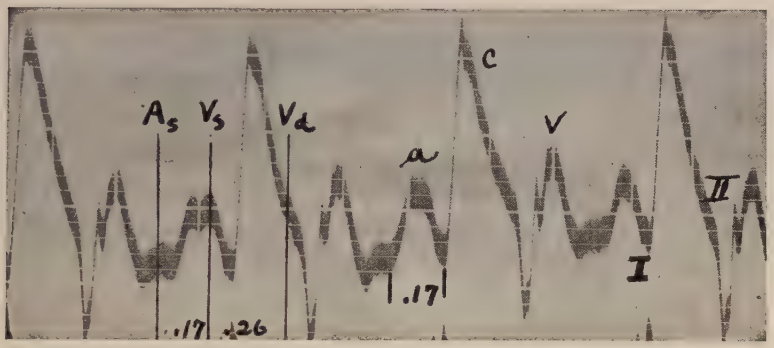

FIG. 53.—Venous pulse tracing from a boy ten years of age recorded photographically by means of a segment capsule. A_s, beginning of auricular systole; V_s, beginning of ventricular systole; V_d onset of ventricular diastole; showing delay in transmission to neck; *a*, a-wave; *v*, v-wave; *c*, c-wave; I, preliminary vibration; II, incisura.

preceding the rise of the diastolic or *v*-wave. The opening of the tricuspid valves early in diastole is evidenced by the summit of the diastolic or *v*-wave.

With these facts in mind it is clear that the venous pulse is of service clinically in that it supplies the following evidence of the cardiac functions: (1) It gives evidence of the presence of an auricular as well as a ventricular contraction. (2) It indicates by the interval elapsing between the rise of the presystolic and systolic waves (commonly called the *a-c* interval) whether auricular and ventricular systoles occur in normal relation to each other; and so, indirectly, as to whether the passage of impulses through the His-Tawara system is delayed or not. Normally the interval does not exceed 0.2 second. (3) It tells us whether or not every auricular contraction is followed by a ventricular contraction and, consequently, whether a complete block of impulses to the ventricles occurs.

The Normal Electrocardiogram.—The normal electrocardiogram shows three distinct upward waves and usually two downward dips

(Fig. 54). Following the terminology of Einthoven, these positive and negative variations are alphabetically labeled P, Q, R, S, and T, although it is now customary to refer to the three positive waves as P, R and T. These electrical variations are due to the fact that, whenever a certain area is conducting an impulse or contracting, it becomes electrically negative to some other resting portion. The bulk of recent work (*Cf.* Wiggers[69]) indicates that the rise of the P-wave is due to the negative wave accompanying the conduction of the impulse across the auricles and the fall may be attributed to a return of the auricular tissue to a normal potential after conduction has ceased. This is followed by an interval during which the impulse is delayed at the *a-v* node and His bundle. As soon as the impulse is conducted to the ventricle by the His-Tawara system, the R-wave rises sharply

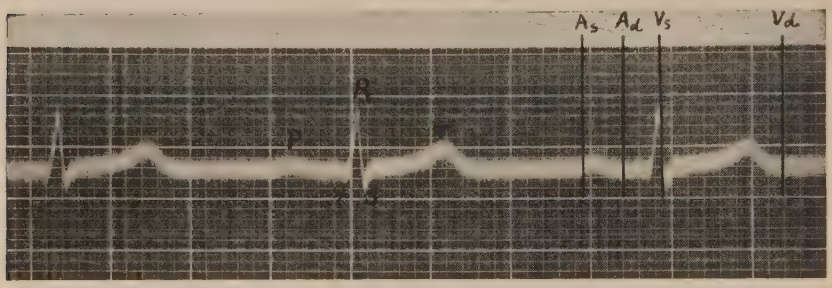

Fig. 54.—Electrocardiogram of an adult, lead II, showing waves, P, Q, R, S, T. Time relations of dynamic events marked on—A_s, auricular systole; A_d, auricular diastole; V_s, ventricular systole; V_d, ventricular diastole. Abscissæ, 1 div. = 0.04 sec., ordinates, 1 div. = 0.2 millivolt.

to its peak (QR) and when the excitation has been completed it falls again to resting potential (RS). When the entire ventricle has been excited to contract, it becomes uniformly negative causing a straight line in the electrocardiogram. Near the end of its contraction, however, the T-variation takes place. The onset of P and the rise of R are separated by an interval of from 0.13 to 0.18 second, the P-R interval, which is required for the impulse to be conducted from the sinus node through the His bundle its branches and terminal arborizations.

In order to obtain an electrocardiogram the heart current is led off from the body by connecting to a string galvanometer either the right and left arm, the right arm and left leg or the left arm and left leg, leads which are designated respectively as Leads I, II, and III.

While the relative size, as well as the absolute time relations of the different waves, varies slightly in the three leads, their general characteristics conform to the above description in normal adults. When, however, the musculature of the right and left ventricle develops in a relatively different proportion than exists in the normal adult heart, or, when one ventricle receives its stimulus before the other, the R-wave of Leads I and II may change its direction and become negative. Thus, if the right ventricle hypertrophies predominantly, or, if this

side receives an excitation earlier than the left, the R-wave is directed downward in Lead I; whereas, if the left side is hypertrophied or receives its stimulus early, the R-wave is directed downward in Lead III.

Electrocardiograms of normal children of all ages have been recorded by a number of investigators, among them Nicolai and Funaro,[50] Lewis,[42] Hecht,[23] Noeggerath[52] and Krumbhaar.[39] These results which are indicated in Fig. 55 show that during the early period of infancy the waves of the electrocardiograms agree with those of adults, but that the R-wave in Lead I is negative, indicating that the musculature of the right side is *relatively* more developed than in adults. This is in exact agreement with the anatomical fact that, at birth, the musculature is equally developed in both right and left

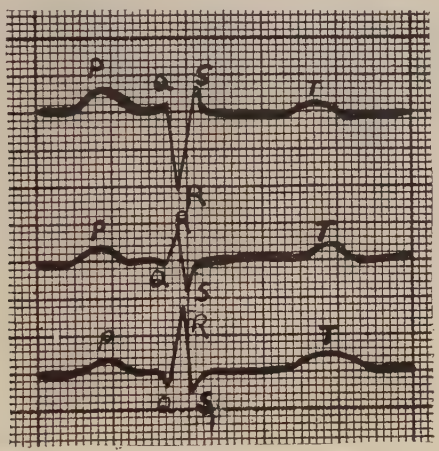

FIG. 55.—Changes in the electrocardiogram, lead I, during the first year. Upper curve, at birth; middle curve, at two or three months; lower curve, at six months.

ventricles. By the second or third month, however, the left side, upon which the work of maintaining the systemic circulation has devolved, has begun to increase in bulk and has definitely exceeded the right in growth (Müller[49]). At this time the electrocardiograms begin to alter their contour. The R-wave is directed upward in Lead I but is followed by a deep S-wave. At six months of age the upward R-wave alone persists, the S depression being no deeper than is found in adults. After this age, then, the electrocardiograms of children do not differ from those of adults unless we stress the observations of Krumbhaar[39] that the Q-depression in Leads II and III is usually more pronounced and the P-R interval is shorter. Occasionally, however, the usual left sided preponderance does not take place in children, as is indicated by the observations of Bridgman[4] who in 10 patients between 11 and 20 years of age found a negative R-wave in Lead I.

The Functions of Contractility and Irritability and Their Derangements.—The contractile syncitium of the auricles and ventricles displays a number of interesting physiological phenomena which differentiate it from skeletal muscle. Unlike the latter, the cardiac syncitium in similar states of irritability responds with the same degree of contraction to weak and strong stimuli. This property, first discovered by Bowditch[3] and by him called the "law of all or none" can probably be attributed to the syncitial nature of cardiac tissue, by virtue of which impulses reach every contractile element and cause them to react to their fullest extent. The only way in which the strength of the cardiac contraction may be increased or decreased is through a change in the irritability of cardiac tissue. This may be accomplished by influences acting directly upon the cardiac muscle or through the agency of nerves. The amplitude of contraction may thus be increased by heat, as in fevers, or decreased when the body temperature falls. It is dependent upon the degree of stretching created by the pressure in the coronary arteries and within the ventricle—the greater these pressures the more vigorous the contraction. It is depressed by oxygen deficiency but at first stimulated and later depressed by the accumulation of carbon dioxide and lactic acid. In doubtful cases of beginning asphyxiation, a strong heart beat is, therefore, no indication of a favorable prognosis. The extent of contraction is modified by many glandular secretions normally and pathologically gaining access to the blood. Bile and pituitary extracts depress the contraction while epinephrin markedly increases it. In addition, cardiac contraction is modified by many drugs, a discussion of which would be out of place here. All of these influences, it should be emphasized, modify the amplitude of contraction, not by supplying a greater stimulus to the heart, but by increasing or decreasing the irritability of the heart syncitium so that it can react with a different degree of contraction *to the same stimuli supplied rhythmically from the venous region of the heart.*

Another peculiarity of cardiac tissue consists in the fact that it is not irritable during contraction. If the ventricles or auricles receive a second stimulus while in the act of contracting, they give, not a more vigorous contraction as is the case in skeletal muscle, but remain non-irritable. This is called the refractory period of the heart (Kronecker,[38] Marey[46]). If a second stimulus is applied during the relaxation, however, the heart responds with another contraction, the size of which depends on the interval after the completion of the preceding contraction. This "extra contraction" or "premature contraction" is of special clinical interest, as abnormal stimuli frequently develop in the auricles and ventricles and produce a form of cardiac irregularity characterized by the rapid occurrence of two beats followed by a pause and then a vigorous beat—a symptom complex of which the patient is frequently conscious. The physiology of such an arrhythmia may be briefly stated as follows: The ventricles normally contract regularly because they receive impulses from the sinus node at fairly

regular rhythmic intervals. If an extra excitation originating in the ventricles suddenly causes a premature contraction, then the next normal impulse from the sinus node comes during the refractory phase of the ventricle and fails to cause a contraction. The relaxation of the premature beat comes earlier, however, hence a pause results until the succeeding normal stimulus again excites the ventricles. In this way the *rate of the ventricles is unaltered* and the pause is therefore designated as the *compensatory pause.*

Instead of originating in the ventricles, the extra stimulus may originate in the auricles causing a premature beat of both auricles and ventricles. The irregularity thus produced differs from the preceding type in that no compensatory pause follows the premature beat, and if frequently repeated the *ventricular beat is thereby increased.*

Both forms of extrasystole produce typical deviations in the waves of the venous pulse and in electrocardiograms, by which they may be differentiated clinically (Fig. 56, I and II). In the case of a ventricular extrasystole, the venous pulse shows premature *c*- and *v*-waves without any preceding *a*-wave. These are followed by a long compensatory pause after which the normal rhythm is resumed. If the extrasystole originates in the auricles, on the other hand, the normal *a*-*c*-*v*-wave sequence is maintained throughout but an entire group occurs prematurely. The electrocardiogram likewise differentiates between auricular and ventricular extrasystoles but has the further advantage of offering an indication as to whether the impulse arises on the right or the left side. In case of an auricular extrasystole, the entire PRT complex merely occurs prematurely and the only distortion that results is that the P-wave may be superimposed on the T-variation of the previous cycle. If the premature stimulus arises in the body or appendage of the right auricle or in the left auricle, the impulses are conducted reversely across the auricles and the P-wave is consequently negative. When the extra stimulus arises in the ventricles the P-variation may be absent or delayed and the R-variation becomes markedly altered in its conformation. It becomes larger and the ascending and descending limbs are more widely separated (Fig. 56, II). The direction of the QRS-complex in different leads is determined by the side upon which the stimulus arises. If it originates in the left ventricle, the QRS-complex is directed upward in Lead I and downward in Lead III. If it originates in the right ventricle, the QRS-complex is directed downward in Lead I and upward in Lead III.

The Function of Conductivity and Its Derangements.—The clinical importance of the His-Tawara conducting system is closely associated with certain peculiarities of conduction manifested by that system. It is apparently necessary for normal conduction that a certain minimal number of fibers be retained. If, for example, any portion of this bundle is slightly compressed, partially cut or destroyed, so that some fibers are not functionating, a peculiar state of conduction characterized as "partial block" is established. The

bundle under these conditions allows some of the impulses to pass but completely blocks one or more of the impulses at comparatively regular intervals. If the fibers of the common trunk in the His bundle are thus affected, the ventricles may, for example, follow three sinus impulses regularly but the fourth ventricular beat will

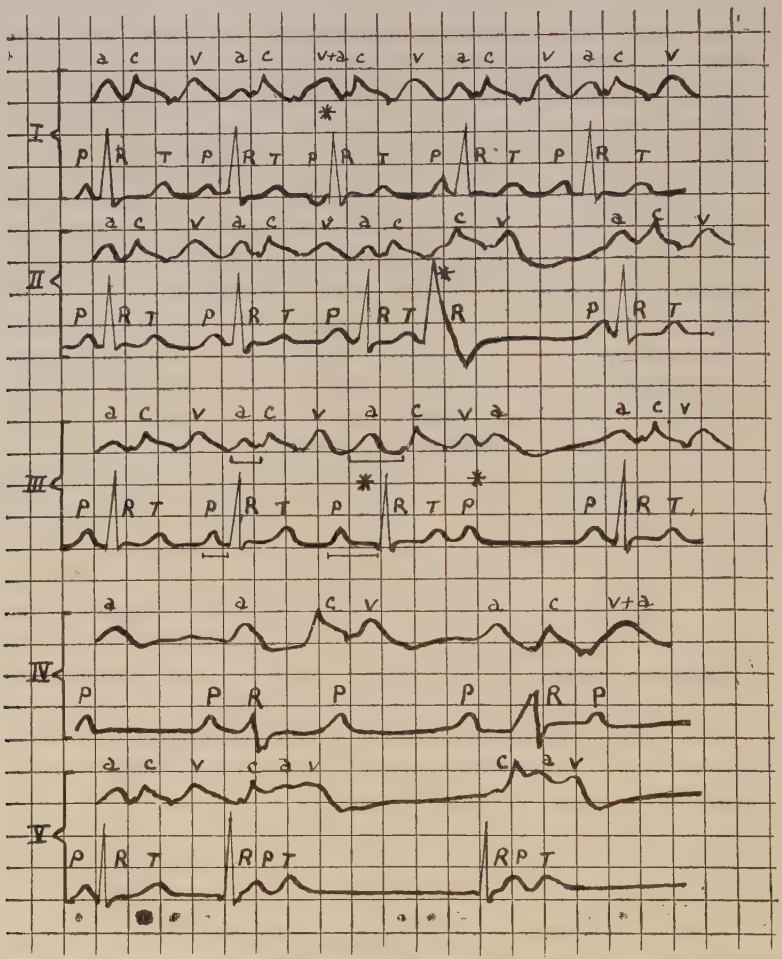

FIG. 56.—Schematic chart of types of venous pulses and electrocardiograms characteristic of a number of cardiac arrhythmias. I, auricular extrasystole; II, ventricular extrasystole; III, partial block; IV, complete block; V, nodal rhythm. *, indicates where abnormal beats occur.

be omitted. As the auricles then beat four times to every three beats of the ventricle, the condition is spoken of as 4 : 3 block. Similarly a 2 : 1 block, a 4 : 1 block, etc., may be established. This condition of partial block can not only be produced experimentally, but frequently occurs clinically when serous exudates, lymph cell accumulations or fibroid changes act to compress the bundle, thus

resulting in an arrhythmia of the ventricular beat and an irregularity of the pulse.

The occurrence of partial block may be detected by the aid of the venous pulse or electrocardiogram (Fig. 56, III). The venous pulse shows a regular sequence of *a*-waves but at regular intervals *c*- and *v*-waves fail to follow an auricular wave. The electrocardiogram also shows a series of P-waves but during the blocked beat a regular RST-complex fails to occur. In some cases the transmission of impulses that do reach the ventricle is delayed, resulting in a lengthening of the *a-c* interval in the venous pulse and of the PR interval of the electrocardiogram.

If the compression of the main bundle, whether due to experimental procedures or to pathological* conditions, prevents all impulses from passing to the ventricle, *complete heart block* occurs. In this case the auricles continue to beat at their normal tempo, but the ventricles assume a slow rhythm entirely unrelated to that of the auricles. Usually the ventricular rate does not exceed 40 or 60. One case that the writer had occasion to study showed a ventricular rate of only 18 per minute.

The venous pulse in such instances shows a regular sequence of *a*-waves and a haphazard sequence of *c*- and *v*-waves unrelated in time to the auricular beats. Similarly, the electrocardiogram consists of regularly spaced and prominent P-waves but the RT-variations occur at intervals entirely unrelated to the P-waves (Fig. 56, IV). In some cases the R-waves are normal in their appearance but usually they become broad and the S-depression deep. The complete block may occur not only in the main branch of the conducting system but also in one of its branches, either left or right. In the latter case the blocked side receives its impulse through the ventricular muscle of the other side and consequently contracts somewhat later, providing the only instance in which asynchronism of the ventricles occurs.

In these instances, the side affected by the block may be ascertained by a study of the electrocardiogram. Thus if a right branch of the bundle is affected, the peculiar, broad ventricular QRS-complex is directed downward; if a left branch of the bundle is affected it is directed upward. Moreover, these aberrant complexes are definitely preceded by a P-wave of auricular origin while the direction of the T-variation is opposite to QRS.

Impulse Initiation and Its Abnormalities.—The physiology of impulse initiation bears directly upon the clinical question of phasic irregularities of the whole heart, the most common form of arrhythmia in normal children between 5 and 12 years of age. Its occurrence ence is so frequent in fact that it may be regarded as a physiological arrhythmia. This variation is produced when the vagi nerves periodically inhibit the rate of impulse formation in the sinus node. As

* Note.—Such blocks are frequent accompaniments of acute infections in children and there is evidence that they may in some instances be congenital.

a rule, but not always, this slowing occurs synchronously with expiration so we may call it a *respiratory arrhythmia*, the heart accelerating in inspiration and slowing during expiration.

It is interesting to note further that the sinus node is by no means the only locality in which impulses may be initiated. If this node is cooled, excised or destroyed by toxic substances, it can no longer remain the pacemaker of the heart. In this case, the auriculoventricular node which is the upper terminal knob of the His bundle takes over the function of initiating the beat. Then the heart becomes slower. The auricles and ventricles receive their impulses at the same time or the ventricular beat may precede that of the auricle. This condition is spoken of as *nodal rhythm.* In such cases the P-wave of the electrocardiogram follows instead of precedes the QRS-complex (Fig. 56, V). Such instances have been found in adults and Lewis and Allen[43] report a case in a child of four and one-half years.

The Physiology of the Cardiac Nerves and the Intracardiac Ganglia.—It is well established by anatomical as well as by experimental studies that the heart is supplied by two sets of nerve fibers—those of the vagus and those of the sympathetic system. Moreover, the auricle contains numerous groups of ganglion cells, the axones of which are distributed to various parts of the auricle and ventricle as well. They reach the ventricle partly through the His-Tawara bundle but to a much greater extent by passing over the *a-v* septum directly to the ventricle. Inasmuch as the specialized cardiac muscle in different regions is self-sufficient to carry on all the functions of the heart, it becomes necessary to inquire into the nature and purpose of this additional nervous mechanism. The intracardiac ganglion cells are of extracardial and indeed of ectodermal origin. Originally situated in relation to the sixth, seventh and eighth cervical and upper thoracic segments of the embryo, they wander toward and into the cardiac mesoblastic tissue. By the sixth week the cells have reached their destination, increased in number, developed fibers and established connections across the *a-v* junction (His, Jr.[29]). They are stopped in their migration by the formation of dense connective tissue at the *a-v* junction which accounts for their predominant supraventricular position (His, Jr.[29]). As the coronary vessels and the *a-v* bundle develop, carrying the connective tissue with them, these axones of the ganglion cells find a path of reduced resistance and in this way reach the ventricle. The intracardiac ganglion cells develop in connection with sympathetic strands with which they are presumably also in functional connection. Animal experimentation indicates that while the impulses supplied to the heart through these extracardiac nerves are incapable of initiating any function of the heart directly, as is the case of motor impulses to skeletal muscles, they modify the inherent functions of the heart. In general terms, the vagus may be said to depress or inhibit all functions of the heart while the accelerator nerve augments them.

Influence on Heart Rate.—Stimulation of the sympathetic fibers causes, in experimental animals, an acceleration of the heart rate hence, it has been termed the accelerator nerve by physiologists. This accelerating influence is continuous in animals, for cutting the nerves causes a slowing of the cardiac rate. It is not known whether such an accelerating influence is present at birth and during infancy, nor is it certainly known to what extent this mechanism is of importance in adults. There is evidence to show that stimulation, in some instances at least, does not increase the heart rate by stimulating the rate of impulse initiation but by increasing the irritability of the *a-v* node to such an extent that it begins to generate impulses more rapidly than the sinus node, thereby becoming the pacemaker of the heart.

Stimulation of the vagus nerve causes a slowing of the heart and it has therefore gained the name of the inhibitory nerve. Its slowing has been shown to be due to the fact that the fibers act through intermediary ganglion cells to depress the rate of impulse formation at the sinus node. A similar influence is constantly exerted by the vagus in adults, in whom the inherent rate is thereby reduced. To judge from the rapid heart rate in infancy, its gradual decrease during childhood, and the fact that atropin does not accelerate it in children, the vagus influence has not developed in early life but is acquired gradually. The figures for the average heart rate at different ages may, in fact, serve as an index of the extent to which this vagal effect over the heart has developed. The development of vagus influence varies markedly and in some cases vagal tonus always remains low so that in adults normal rates of from ninety to one hundred are found.

Vagus tonus in adults becomes decreased in a variety of conditions so that a cardiac acceleration results. Among these may be mentioned psychic disturbances, exercise, meals, intestinal disturbances, etc. It is important to note that these influences tending to accelerate the heart by reducing the tonic activity of the vagus center cannot operate in infancy and only to a slight degree in early childhood, consequently, variations in heart rate corresponding to those of adults are not to be expected. Many influences, however, are able to directly affect the sinus node in childhood, among which an increase in temperature may be mentioned; but the percentile increase in heart rate due to this condition is not as great as in the adult in whom the loss of vagus inhibition also plays a part.

Influence on Conductivity.—The vagi nerves also contain fibers that affect the conduction of impulses. Some fibers apparently end around cells in the conducting system and so are capable of producing a condition of partial or complete *a-v* block. In some animals these fibers run particularly in the left vagus, stimulation of which may result therefore in a slowing of the ventricular rate without any interference with the auricular rhythm. Some instances of block have indeed been shown to be due to such a functional rather than an anatomic cause. A functional block may be differentiated by the use

of atropin which, by paralyzing the vagus terminals, causes this type of heart block to disappear.

Influence on the Amplitude of Auricular and Ventricular Contraction.—The vagus nerve exerts a depressant effect on the contractility and irritability of the auricles, consequently the amplitude of their contraction is reduced during vagus stimulation. As no such effect is seen in the ventricles, but, on the contrary, an augmentation of their contraction takes place, it is probable that the vagus fibers establish no direct connection with the ventricular muscle. The increased amplitude may be satisfactorily accounted for by the longer rest period during the simultaneous slowing of the rate.

The accelerator fibers upon stimulation, on the contrary, augment both the auricular and ventricular contractions, indicating that these fibers exert a stimulating influence upon the ventricular as well as the auricular muscle.

The Dynamics of the Circulation.—It is the dynamic function of the systemic circulation to supply the tissue cells with oxygen and nutrient materials and to relieve them of carbon dioxide and waste products. Regarded from the standpoint of the capillaries where an interchange of substances with the body cells goes on through the thin endothelial cells, the systemic circulation must be divided into a distributing and a collecting system. The former includes the ventricles, arteries and arterioles; the latter comprises the venules, veins and right auricle. Anatomically, each portion of this system is admirably adapted to the function it is required to perform. The ventricles, which serve as the force pump, are thick-walled muscular structures; the larger arteries and their branches, which are required to accommodate varying quantities of blood, are composed largely of elastic connective tissue; the arterioles, which take the role of stop-cocks controlling the flow to the capillaries, contain many circular muscular fibers under the control of vasomotor nerves capable of widening or contracting their lumen.

As the capillaries are approached, the size of the individual vessels becomes progressively smaller thus increasing the resistance to the flow of blood, but the total cross-section increases markedly thereby supplying a wide stream bed in the peripheral vessels. As the blood is collected by the venules and veins, the total cross-section progressively decreases again.

In order to replenish the oxygen volume of the blood and the nutrient materials, two special subcircuits exist, the pulmonary and portal systems. The former conveys the venous blood from the right ventricle by a distributive system to the lung capillaries, where an interchange of oxygen and carbon dioxide with the alveolar air takes place. The latter conveys the blood through the splanchnic vessels to the intestinal capillaries where absorption of food materials takes place. From these vessels the blood is collected by the portal vein which carries it to the liver. Here a second set of capillaries are found

through which the splanchnic blood must pass before it is returned to the vena cava by the hepatic vein.

In this complex system it is the function of the ventricles to supply the power which pumps the blood from the collecting systems to the distributing systems, under sufficient pressure to insure a continued flow through the capillaries. To accomplish this, requires that the heart muscle contract with efficiency and, as in a gasoline engine, that the valves not only close efficiently but are properly timed. While the mechanism of the heart pump follows many of the physical laws of a force pump, the fact that it is a living machine, capable of changing its constants, necessitates a special consideration of its dynamics.

Method of Analyzing the Dynamics of the Heart.—Physically, fluid is moved from one portion of the circulation to another by a differ-

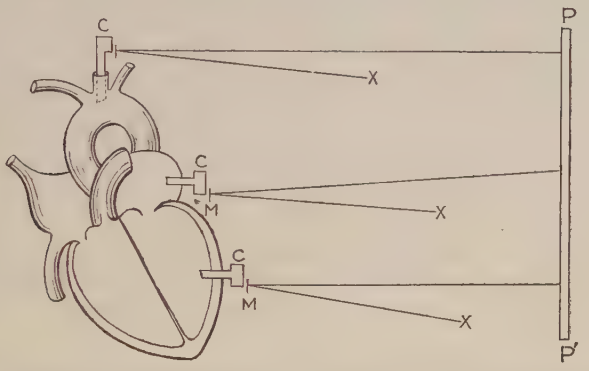

FIG. 57.—Scheme showing principle of apparatus for recording pressure changes in the heart and large vessels photographically. *C*, capsules introduced into cavities and vessels; *M*, mirror on rubber membrane; *X*, light beam; *P-P'*, sensitive photographic surface.

ence in pressure in the two places. Consequently, if the variations in pressure in the auricles, ventricles and arteries are simultaneously recorded, it is possible to formulate the precise dynamics of the heart and circulation. The apparatus required for this purpose is described elsewhere by the writer[66] but the principle of this apparatus may briefly be explained. Suppose that a small fluid-filled cannula covered by a tense rubber membrane is inserted through the auricular and ventricular walls and into the aorta as shown in Fig. 57. Each membrane will then respond to every variation of pressure within the heart and aorta. If a small mirror is attached to each rubber surface these membrane movements can be made visible and magnified by reflecting a beam of light from each mirror. By allowing these beams to focus upon a moving plate or sensitive film a true picture of the pressure variations can be obtained.

In Fig. 58 are shown the variations of pressure occurring under normal conditions in the auricles, ventricles, and aorta, together with a curve showing the changes in the volume of the ventricles during

systole and diastole. From a study of such tracings it is possible to formulate precisely the dynamic sequence of events.

Sequence of Events during the Cardiac Cycle.—All portions of the two ventricles are excited simultaneously. As the semilunar valves are closed the pressure within the ventricles increases and first closes the auriculoventricular valves, after which it continues to rise sharply until it exceeds the pressure in the aorta. When this occurs, the semilunar valves are opened and blood is ejected into the aorta. *Systole*, accordingly, may be divided into an *isometric period*, during which the pressure rises while the auriculoventricular and semilunar valves are both closed; and an *ejection period*, during which the semilunar valves are open and blood is ejected into the aorta. During this stage ventricles and aorta form a common cavity. At the beginning of *diastole* the pressure within the ventricles falls rapidly, consequently the semilunar valves close almost immediately. When the pressure within the ventricles has fallen below that then existing in the auricles the auriculoventricular valves open and blood flows rapidly into the ventricles. Further events depend on the duration of diastole. If the heart rate is slow and diastole long, the period of rapid ventricular filling is followed by an interval during which little or no blood enters the ventricles, the period of *diastasis*. If the heart rate is rapid and diastole short, this period of stasis is abridged or absent. Toward the end of diastole the auricles contract and add another small increment to the ventricular filling. *Diastole* may then be divided into a *period of rapid filling*, a *period of diastasis* and *auricular filling*.

Factors Determining the Dynamic Efficiency of the Ventricles.—The dynamic efficiency of the ventricles is determined to some extent by the inherent state of muscular irritability. In the normal circulation, however, this plays a minor rôle. Here the efficiency of the ventricles during systole is largely determined by the dynamic conditions obtaining during the previous diastole. In other words, the systolic ejection is determined by the diastolic filling (Henderson[24]). This filling is determined less by the actual capacity of the ventricles than by the effective venous pressure and by the duration of diastole. In adults and during the major portion of childhood the venous pressure is apparently sufficient to complete four-fifths of the entire filling during the early period of diastole (Henderson[24]). Very little is added during the period of diastasis but when auricular contraction occurs it contributes the additional one-fifth to ventricular filling. The effect of this dynamic arrangement is, that the systolic discharge is not reduced materially unless the heart accelerates so much that the period of early diastolic filling is affected.

An adequate circulation of blood requires not only the ejection of a proper quantity of blood but its injection into the aorta under sufficient pressure to maintain an adequate capillary flow during diastole. In other words, the heart must be efficient as a force pump as well as a meter of the circulation. This mechanism is also controlled by the

venous pressure. As soon as the ventricles have been filled during the early portion of diastole, the pressures within the auricles and ventricles become equal. As a matter of fact the flow from auricles to ventricles ceases because such an equalization has taken place. As blood continues to flow into the continuous auriculoventricular cavities, the pressures within both cavities continue to increase. Upon the height of this pressure at the end of diastole the height to which the intraventricular pressure rises, during the next systole, depends (Wiggers)[67] (Starling and Patterson[53]). The higher this venous pressure, the higher the pressure within the ventricle and aorta rises during the next ejection. This is due to a property common to all muscular tissue—a slight increase of tension on muscular fibers before contraction enhances the irritability so that they respond with a larger contraction. It is evident that the systolic discharge as well as the energy with which blood is ejected is thus automatically controlled by the venous pressure. If the volume of venous blood returned to the heart at any time becomes greater than normal it is ejected in larger quantities and with greater force; if it becomes reduced, the reverse is the case.

The Dynamic Functions of the Auricles.—Before the valvular structures and septa of the heart have developed fully and while the trabecular layers of the ventricles constitute the chief contractile mechanism, the auricles probably play a prominent part in filling the single chambered ventricle. As soon as development is complete they serve the purpose of filling the ventricles less and less. In the adult heart they act as terminal reservoirs for the returned venous blood. In addition, however auricular contraction serves to elevate the intraventricular pressure and so aids the mechanical stretching of the ventricle which favors a more forcible ejection. According to Henderson and Johnson[25] it also acts to produce an apposition of the auriculoventricular valves, which is of real value when the a_s-v_s interval is short (Dean[11]). Furthermore the auricle serves as a reserve mechanism in pathological conditions. Thus it has been found that whenever ventricular filling cannot be readily accomplished by the force of the venous pressure alone, then auricular contraction contributes more to this filling. This is the case in mitral stenosis (Hirschfelder[27]) and during hemorrhage (Wiggers[68]).

Pressure Changes in the Arteries and Peripheral Blood-flow.—As blood is injected into the aorta during systole the pressure is sharply elevated. During the early portion of systole, the pressure continues to rise, though less steeply (Fig. 58, *C*). This is due to the fact that during this interval more blood is injected into the aorta than flows out of the peripheral arterioles into the capillaries. Soon the pressure begins to fall, however, indicating that now the peripheral outflow exceeds the central injection. At the beginning of diastole the pressure rapidly falls within the ventricle and causes the closure of the semilunar valves. These events are marked on the pressure curve as a sharp drop and after-vibration (Fig. 58 *C*, 6–6′). During diastole

the blood stored in the large arteries during the preceding systole gradually flows from the arterioles into the capillaries, causing the pressure to gradually fall until the next systole. The highest level to which pressure is raised in mid-systole (Fig. 58 *C*, 5) is by definition, designated as the *systolic pressure.* The lowest point to which it falls during diastole[1] is designated as the *diastolic pressure.* The difference between these pressures is called the *pulse-pressure.*

The systolic and diastolic pressures are determined, to a considerable extent, by the rate of the heart and the systolic discharge; in

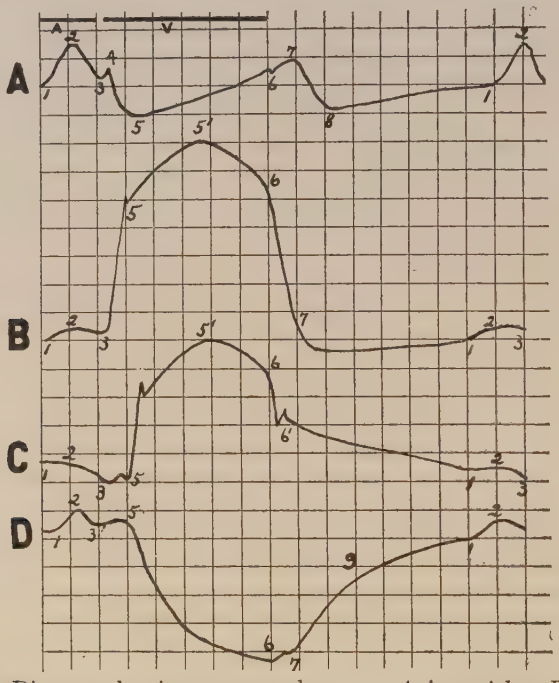

Fig. 58.—Diagram showing pressure changes. *A*, in auricles; *B*, in ventricles; *C*, in aorta; and volume curve of ventricles, *D*. *A*, auricular systole; *V*, ventricular systole. 1, 2, 3, pressure and volume changes during auricular systole; 3–5, during isometric period of ventricles; 5–6, during ejection period of ventricular systole; 6–7, during early diastolic relaxation of ventricle; 7–9, diastolic filling of ventricles; 9–1, diastasis.

short, by the minute output. These two factors do not influence both pressures equally, however. Thus, an increase in heart rate increases the diastolic pressure more than the systolic and consequently reduces the pulse-pressure; while an increase in systolic discharge increases the systolic pressure more than the diastolic pressure and therefore increases the pulse-pressure. Under both conditions the volume flow of blood through the capillaries increases.

An increase in systolic and diastolic pressures may be produced also by a change in the peripheral resistance. The walls of the smaller arterioles are abundantly supplied with vasomotor nerves which upon

stimulation cause a marked reduction in their caliber and consequently a considerable increase in resistance. This elevates systolic pressure less than diastolic and reduces the pulse-pressure. Under these conditions the capillary volume flow is decreased, however. Hence it follows *that the flow through the capillaries is not necessarily determined by the height of the pressures nor can it be directly gauged by the value of the pulse-pressure.*

The Compensatory Mechanisms of the Circulation.—It is apparent, according to dynamic laws, that every alteration in the rate and output of the heart as well as every variation in the peripheral resistance results in an alteration in blood pressures. Such, however, is not the case in the body. Under normal conditions, the blood pressures have a tendency to remain remarkably constant. This is made possible by the operation of certain compensatory mechanisms. If the arterial pressures have a tendency to increase and the pulse-pressures to decrease due to a more intense vasoconstriction, reflexes are set up from the large blood vessels and root of the aorta which slow the heart and reduce its minute volume, thus tending to maintain normal pressure relations and restore the pulse-pressure to normal. A converse coöperative action occurs when the blood pressure is reduced owing to a low peripheral resistance. If the blood pressure is reduced because blood is extracted from the vascular channels, as in hemorrhage or shock, the heart accelerates and the peripheral vessels constrict in an effort to elevate the pressure. In these and other similar ways the compensatory mechanisms of the circulation are adjusted to prevent great fluctuations in the arterial pressures. When pressure relations are decidedly abnormal we may therefore conclude either that some circulatory derangement exists which is more pronounced than the pressure variations actually indicate, or that the compensatory mechanisms are deranged.

The Interpretation of Circulatory Conditions in Childhood.—Many facts gathered from experimental physiology can unmistakably be transferred to the circulation of children and adults. It is apparent, however, that in many instances the mechanism of the circulation is determined largely by the physical or physiological state of its structures. As this may conceivably be different in operated animals and in normal man, and indeed may vary during different periods of childhood, it is evident that many experimental facts cannot be so clearly applied. In such cases, we have long been forced to be content with applying the general laws and principles derived from experimental work to the human circulation. With the development of newer methods by which certain phases of the circulation may be directly studied in man, many processes that hitherto remained ambiguous may be more precisely analyzed. Thus, if the character of the pulse contour or normal electrocardiogram at different ages be known, we can understand the existing cardiac physiology precisely because experimental work has demonstrated the exact cardiac mechanisms that invariably accompany such curves. Unfor-

tunately, however, only those data in regard to the circulation which are capable of study by the unaided senses or by very simple mechanical appliances have been extensively studied in children. The functions which require the employment of more elaborate apparatus have either been investigated very imperfectly or not at all.

The author, upon whom falls the task of presenting a concrete picture of the circulation during different periods of childhood, cannot refrain from emphasizing this unfortunate hiatus in our knowledge of the circulation, not only because it is manifestly necessary, in certain instances, to present a probable rather than quite certain and final picture of the circulation; but also because the necessity for a more thorough study of these accessible functions by newer methods of investigation should be urged upon those to whom time and opportunity for their study is vouchsafed.

With these facts in mind, we may proceed to analyze to what extent our conceptions of the physiology of the circulation during infancy and childhood may be guided by direct evidence.

Heart Rate.—When the heart sequence is normal, the cardiac rate is a criterion of the rate of impulse initiation in the sinus node. The rate may be determined in children of all ages by palpation of the radial artery, palpation of the apex beat or auscultation of heart sounds. The latter procedure is more certain in the case of cardiac irregularities, in which case, owing to abortive contractions, a pulse wave may fail to reach the radial artery and so cause a *pulse deficit.*

Observations show that the pulse rate varies considerably in different children of the same age, height and weight; even when such modifying influences as excitement, exercise, meals, etc., are taken into consideration. This is shown in the following table based on an analysis of 934 children (Vierordt[62]):

MAXIMUM AND MINIMUM HEART RATES AT DIFFERENT AGES

Age, Years	Maximum Frequency	Minimum Frequency
0–1	134.0	101
1–2	110.6	84
2–3	108.0	84
4–5	103.0	80
5–6	98.0	70
6–7	92.1	72
7–8	94.9	72
8–9	88.8	72
9–10	91.8	68
10–11	87.9	56
11–12	89.9	60
12–13	87.9	67
13–14	86.8	66

Average figures compiled from many observations at the same ages tend to show that a progressive decrease in heart rate occurs until adult life is reached. The heart accelerates immediately after birth but recovers its prenatal rate within an hour. During the first year, the

rate slows gradually until at the end of the first year the heart rate may be said to average about 120 per minute. At five years of age the heart rate is rarely above 100 and by the ninth year is usually less than 90. Further details may be gleaned without further comment from the tables preceding and following.

PULSE FREQUENCIES DURING FIRST YEAR (AFTER VIERORDT)

Age	Rate
Fetal	130–146
At birth	180
10 min. after	170
15 min. to 1 hr	134–136
1 day	123–126
1 to 8 days	124–125
1 week	124–130
2 weeks	133
3 weeks	131.4
2 mos	130–133
2 to 6 mos	113–130
6 to 12 mos	113–127

Statistics also show that there is a relation between the height and weight and the heart rate in children of the same age, in the sense that the heart rate tends to be slower in children of larger stature. This is shown in the following table:

RELATION OF HEART RATE TO BODY LENGTH AT DIFFERENT AGES
VOLKMANN

Age	Small Children	Large Children
1	146.5	123.1
2	124.0	111.0
3	113.2	104.3
4	111.7	110.2
5	106.0	102.3
6	102.5	99.9
7	101.0	93.8
8	97.0	98.0
9	90.0	89.0
10	93.0	88.0
11	88.5	85.9
12	91.3	81.0
13	87.6	81.0
14	89.5	89.3
15	81.0	81.0

According to Rameaux[62] this relation of heart rate to body-weight is so constant that the rate may actually be calculated for any age by the formula $R = \frac{167.5}{\text{Lngth}}$. Volkmann,[62] however, maintains that this formula applies only to the early years of rapid growth.

Cardiac Rhythm.—The heart is irregular in a large percentage of children whose cardiac action must be considered normal. This

is shown, for example, by an analysis of the cardiac rhythm in 321 school children between the ages of 5 and 14, reported by Friberger.[18] In 12.2 per cent. of these cases a marked irregularity and in 50.4 per cent. a moderate arrhythmia was found. Cardiac irregularity may be transient, disappearing and reappearing from time to time. If there is any tendency for its existence it is usually manifested during rest and disappears during activity when the heart accelerates. Frequently it is present only during sleep and disappears upon awakening as the author has had occasion to observe.

As a rule the irregularity is of sinus origin and brought about by a periodic activity of the vagus over the heart. It seems that as vagus control over the heart is gradually acquired during childhood, it is exerted periodically and not constantly. Even in adults, where the heart seems perfectly regular to our unaided senses, this periodic activity persists to a certain extent so that if the pulse curves are accurately analyzed they show variations from beat to beat. Such sinus arrhythmias are therefore physiological and of no pathological import.

Occasionally other forms of irregularity are found in hearts that otherwise appear to be perfectly normal. Among them extrasystoles of both auricles and ventricles are not uncommon (Halsey,[21] Visco,[63] Wilson[71], etc.). Heart block, however, probably is never to be considered as normal. It is frequently present during acute infections and occasionally persists after them. Such cases have been reported in children by Armstrong and Mönckeberg,[1] Cleveland,[8] Hecht,[22] Hutchinson and Parkinson,[32] Lewis and Allen,[43] Magnus-Alsleben,[47] Pisek and Coffen,[54] Whipham[65] and others.

The Arterial Pulse.—The arterial pulse is caused by an expansion and relaxation of the arteries with each variation of pressure within the arteries. Consequently, if a record of the pulse is taken from the large arteries of the neck (*e.g.*, the subclavian of lower carotid arteries) by optical capsules, the tracings show all the characteristics of the pressure curves recorded from the aorta. As shown in Fig. 59, *A*, it shows the following details: A preliminary wave occurring during the isometric period of the ventricle (1–2); the primary wave due to the sudden ejection of blood (2–4); the systolic rise and fall of pressure during the ejection period (4–6); the incisura, marking the onset of diastole and closure of the semilunar valves (7–8); and the diastolic decline of pressure (8–1).

Clinically the pulse tracing taken from the central arteries is important. It permits an exact determination of the duration of the following ventricular events: The isometric period (1–2), the ejection period of systole (2–7), total systole (1–7), and total diastole (7–1). Its contour gives important information of the relation between cardiac ejection and peripheral flow. This must be analyzed in greater detail. In adults the pressure curve shown in Fig. 59, *A*, may be regarded as the normal type. It shows during the ejection phase first a rise (4–5) and then a gradual decline (5–7) of pressure,

which indicates that early in systole the ventricular ejection exceeds the amount flowing from the peripheral arterioles into the capillaries, but during the latter portion becomes less than the peripheral flow. If the peripheral resistance is reduced, as by vasodilation, a curve similar to that shown in Fig. 59, *B*, is obtained. The pulse wave changes, not only in that the primary wave is more prominent, but the pressure rises slightly (4–5) and then falls markedly (5–7), indicating that the peripheral flow greatly exceeds the systolic ejection during the latter part of systole. *A* third variation is obtained when the systolic discharge is reduced, *i.e.*, in hypodynamic conditions of the heart. The curve then entirely loses the primary wave and shows a slow rise and fall during the ejection period, as shown in *C* of Fig. 59.

The pressure variations taking place in the central arteries are propagated to the peripheral vessels with a velocity of about 6 to 10

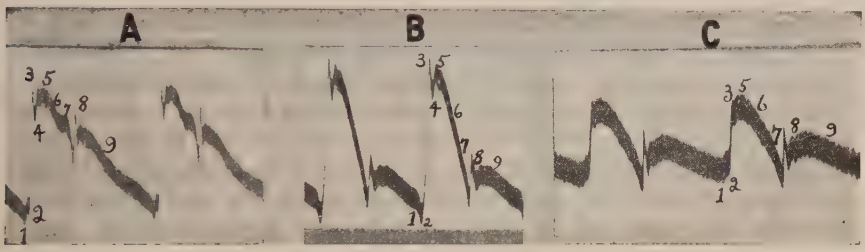

Fig. 59.—Three types of central arterial pulse curves. *A*, normal heart and peripheral resistance; *B*, during low peripheral resistance; *C*, during hypodynamic heart action. 1–2, preliminary vibration; 2–4 primary wave; 4–7, rise and fall during systole; 5, systolic summit; 7–8, incisura; 9, diastolic outflow.

meters per second. Consequently the radial pulse-curve rises approximately 0.15 second later than that in the neck. In its transmission through the yielding and elastic vessels, the details of the pulse-curve, present in the large arteries, are gradually eliminated so that a record of the radial pulse gives neither a true index of the time relations of systole and diastole nor a reliable picture of the dynamic changes in pressure. The graphic registration of the radial pulse, at least by such convenient forms of clinical apparatus as the polygraphs, therefore adds little to the knowledge which may be equally well gained by palpation.

In palpating the radial pulse, attention should be directed to variations in rate, rhythm and character. This latter involves a consideration of its amplitude and its form. The amplitude of the radial pulse is a criterion of the pulse-pressure. As this is modified, not only by changes in the systolic discharge, but also by variations in cardiac rate and by peripheral vasomotor action, the amplitude of the pulse is not a criterion of the efficiency of the ventricles. Thus, a large pulse may occur when the rate is slow, the systolic discharge large or the peripheral resistance low.

By experience, the sense of touch may be developed so that changes in the contour of the pressure wave in the radial artery may, in many cases, be accurately determined. Thus, we can ascertain whether the rise of pressure is rapid or slow and whether the fall is steep or gradual. Occasionally the dicrotic wave may also be palpated. Experience has proven, however, that in detecting the contour of the radial pulse, the palpating finger frequently errs, as may be verified by tracings taken by reliable optical apparatus. Fortunately, this is largely of academic interest and, as explained before, is of no great significance as far as the interpretation of the vascular dynamics is concerned.

The Arterial Blood Pressure.—The highest point to which the pressure rises during the ejection phase and the lowest point to which it falls during diastole are designated *systolic* and *diastolic* pressures respectively. Their difference is the *pulse-pressure*. It is the purpose of blood pressure observations to determine in absolute figures these points which are shown only relatively in pulse tracings. The most satisfactory method by which this may be accomplished is the auscultatory method introduced by Korotkoff. Any form of mercury or aneroid pressure apparatus may be employed. The compression cuff is snugly attached to the forearm. According to Judson and Nicholson,[34] who offer a critical review of the various methods employed, a cuff 9 cm. in diameter is necessary between the ages of four and eight, while a 12 to 14 cm. cuff is required between the ages of 14 and 25. As the application of these cuffs offers considerable difficulty in the cases of younger children and infants in whom the entire upper arm is no more than the required width of the cuff, the thigh has frequently been used (Hill,[26] Hoobler[31]) or a narrower cuff substituted. While the use of the latter apparently gives lower readings, it does not necessarily mean that these are incorrect in limbs of small diameter such as are found in children. Indeed, it is quite as likely that the readings taken with the wider cuff are too high. After the arm-piece has been adjusted a stethoscope is placed about 2 cm. below the constricting cuff over the course of the brachial or femoral artery. The pressure is then pumped up until the peripheral pulse is obliterated and is then allowed to gradually leak out. As the pulse breaks through the cuff to the artery over which the stethoscope is placed, a sound is heard with the first beats. The reading taken at this time represents the systolic pressure. As the pressure continues to fall in the cuff, the quality of the sound changes. Its intensity first increases until it reaches a maximum; then decreases, becomes muffled and finally ceases altogether. Investigators do not absolutely agree as to whether the muffled stage or the entire disappearance of sound more accurately represents the diastolic pressure. The consensus of opinion (*Cf.* Wiggers,[66]) favors the fourth phase as the more accurate criterion, even though this allows a certain latitude in selecting the end-point. No great error is involved, however, if the complete disappearance of sound is taken. Occasionally the auscultatory method is impossible or very difficult

to apply in young children owing to the deep position of the blood-vessels and the fatty paniculus of the skin. In these cases, the oscillatory method of Erlanger or the registration of the peripheral pulse by a pith-ball-cuff applied peripherally to the constricting cuff, as suggested by Hoobler,[31] may be used.

The blood pressure values at different ages have been studied by many pediatricians. Of these only a few can be mentioned. Leitao[41] studied the pressures in 200 infants under one year of age by the Erlanger apparatus. His results are summarized in the following table:

Age	Systolic pressure	Diastolic pressure	Pulse-pressure
2 mos.	68	50	18
3 mos.	78	50	28
7 to 8 mos.	78–84	54–60	20–34

The pressures in older children have been most extensively studied by Judson and Nicholson,[34] who also give a comprehensive review of previous work. A table of their results obtained by the auscultatory method checked by the Erlanger apparatus in 2300 observations on well-nourished children between the ages of 3 and 15 is appended.

Age, years	Cuff width, cm.	Systolic pressure, mm. of Hg	Diastolic pressure, mm. of Hg muffled sound		Pulse pressure
			Sound	Lost	
3	9	92.0	58.9	41.6	33.6
4	9	92.6	61.7	49.1	30.9
5	9	91.6	60.0	46.0	31.6
6	9	93.8	63.5	59.9	30.3
7	9	87.9	64.2	49.2	22.7
8	13	93.0	59.6	41.0	33.4
9	13	91.7	62.2	50.0	29.5
10	13	99.0	64.0	47.3	34.4
11	13	95.8	62.3	49.1	33.5
12	13	99.9	59.6	37.6	40.3
13	13	104.0	63.2	47.0	30.8
14	13	105.8	63.7	48.2	42.1
15	13	99.6	61.8	43.6	37.7

A few general conclusions suggested by the above studies may be briefly stated. Most investigators find that the systolic pressure gradually increases during childhood, while the diastolic pressure changes less. The general statements have it that systolic pressure ranges from 75 to 90 during infancy, increases to from 90 to 110 in childhood and to from 100 to 120 at puberty. In accordance with these observations, the pulse-pressure increases gradually as the heart slows, which conforms to dynamic laws. The extensive recent observations of Judson and Nicholson[34] quoted in the table above apparently do not confirm this commonly accepted gradual increase of pressure. According to them, the systolic pressure increases only very slightly between 3 and 10 years of age. During adolescence, that is, between the ages of 10 and 14, an abrupt increase is found. The diastolic pressure, however, remains practically unaltered throughout childhood, consequently between the ages of 10 and 14, the pulse pressure shows an increase.

The Heart Sounds.—During each cardiac cycle, at least two series of vibrations originate within the heart which are propagated to the wall and cause it to vibrate in unison. By auscultation, they are recognized as the two *heart sounds*. The first sound occurs at the onset of systole and the second at the beginning of diastole. They are therefore of value in determining the systolic and diastolic phases of the heart cycle. It has been shown that the first sound is due to a mixture of the vibrations arising from the muscular contraction of the ventricles and the closure of the auriculoventricular valves, while the second is caused by the closure of the semilunar valves of the pulmonary artery and aorta.

The heart sounds in children differ from those in adults, not only in their more rapid succession, but also in their quality. In early infancy, the systolic interval between the first and second sounds is practically equal to the diastolic interval between the second and first. On account of the thinner chest wall and its closer approximation to the heart, and also because the resonance is greater, the heart sounds are relatively louder and are heard over greater areas of the thorax in children. Owing to the relatively small mass of the contracting ventricular muscle, the first sound at birth and during infancy is largely due to vibrations caused by the closure of the auriculoventricular valves. The first sound is therefore of short duration and not appreciably longer than the second. Its pitch is higher and its quality clear and more musical than in adults. The first sound is distinctly accentuated at the apex, but the second sound, as in adults, is louder at the base of the heart. The second sound is louder over the pulmonic area (Downes[13]).

As the bulk of heart muscle becomes larger and the elastic tissue increases in the ventricular walls, the character of the first sound changes. This change is well marked by the fourth or fifth year. The first sound at the apex acquires what clinicians recognize as a "muscular quality." It becomes more "booming" in character,

its pitch lowers and its duration is longer. The second sound is now louder at the aortic area, but everywhere maintains a high pitch and a clear quality.

Other Sound Vibrations Originating in the Heart.—In older children, especially when the heart is slow, a third sound may be recognized. According to Thayer,[61] it is audible at the apex in 65 per cent. of youths. This sound follows the second and is therefore early diastolic in time. It is very short and much softer than the first and second sounds.

Between the ages of 5 and 15, additional vibrations are frequently associated with the first sound. They may manifest themselves, on auscultation, merely as an "impurity" or they may be of longer duration and are then designated as "functional murmurs." These murmurs may be of short duration and occur early in systole or they may continue throughout the major portion of systole. As a rule, they are loudest over the base of the heart and are transmitted toward the apex and to the large vessels of the neck indicating an origin at the aortic orifice of the heart. Their frequent occurrence and subsequent disappearance makes them of physiological interest.

Upon auscultation over the jugular bulb, a venous hum is also frequently heard in children. This murmur is most pronounced in inspiration and accentuates at the beginning and end of each systole, that is, at a time when the heart is changing its position (Landis and Kaufmann,[40] Coombs[10]).

The Registration of Heart Sounds.—It is the purpose of sound registration to substitute for the ear drums some mechanism capable of converting the sound vibrations into light waves which may be photographed and recorded on sensitive photographic plates or paper. No device has yet been invented that equals in its inherent frequency the human ear. Nevertheless, very satisfactory records have been obtained. Their advantage over auscultation consists in the elimination of the subjective element and the fact that the sounds may be more exactly studied as to their character and precise time relations. Of the many procedures suggested to accomplish this, only two have been found satisfactory. Einthoven developed the method of registering sounds by the use of a microphone in circuit with a transforming coil and a string galvanometer. The improvements in technique and the precautions necessary have beeen recently analyzed by Battaerd.[2]

A simpler and more direct method of sound registration owes its origin to Frank. This method has been recently modified by the writer and Dean[70] so as to render it more sensitive and to protect it from sound vibrations in the room. In brief, the sounds are led to and recorded by a segment capsule of special design (Fig. 60) by a tube in which a lateral opening is left.

Before considering the nature of the sounds recorded by these instruments from the thoracic wall, it is well to consider briefly

the nature of the records obtained by a special form of receiver from various regions of the exposed heart. Sound vibrations are present in all regions of the heart, auricles, ventricles and aortæ. The character of the second sound is essentially identical in all these regions. The first sound, however, differs considerably in various portions of the heart. Briefly, two types of sounds may be described, the ventricular and the aortic.

Under normal conditions, the first ventricular sound begins with a small *preliminary vibration* (*A*). This is followed by a group of irregular *maximal vibrations* (*B*) reaching their greatest amplitude before ejection occurs; and a *final group* of smaller decrescendo waves *C* during the early period of ejection. The first arterial sound also shows a preliminary vibration. (*A*). Then occur two distinct groups of vibrations each of which reaches a maximum. The first group C_1 occurs during the isometric period; the second C_2 during the ejection period. This may be distinctly separated from the first group, giving the sound a reduplicated character, or it may fill the entire period of systole and cannot then be distinguished from a murmur.

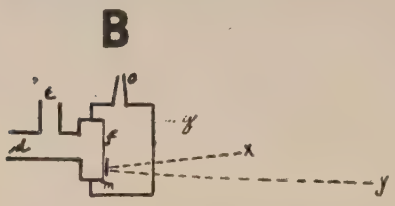

Fig. 60.—Heart sound capsules. *d*, tube connecting with thoracic bell; *e*, side opening; *f*, delicate rubber film vibrating with the sounds; *m*, mirror; *g*, housing with glass front window; *o*, outlet for equalization of pressure; *x–y*, reflected light beams. (Wiggers and Dean.)

All of these characteristics of the first sound are not, as a rule, reproduced in records from the chest wall. The preliminary vibrations and some of the final vibrations of the ventricular sound are usually not transmitted to the chest with sufficient intensity to be recorded. Occasionally, however, they may be recorded in favorable subjects, as was first pointed out by Fahr,[14] and later confirmed by Battaerd.[2] The first aortic and pulmonary sounds are even less well reproduced owing to the greater distance of the aorta and pulmonary vessels from the chest wall. The second systolic component, so characteristically found in direct records from the heart, is usually entirely missing. Battaerd, however, reports its occasional existence in records for which exceedingly sensitive apparatus was used.

We may therefore conclude that a group of vibrations follows the first systolic group but that they are not sufficiently intense to be appreciated by the ear. The author is tempted to suggest that possibly the reduplication of the first sound or the so-called functional murmurs of children heard over the base of the heart may be due to such a normal group of vibrations constantly present in the heart. The fact that they are so frequently found in children and absent in adults may well be due to the thinner chest wall, the closer anatomical relation and better resonant qualities of the thoracic cavity in children. Records from the thoraces of children would

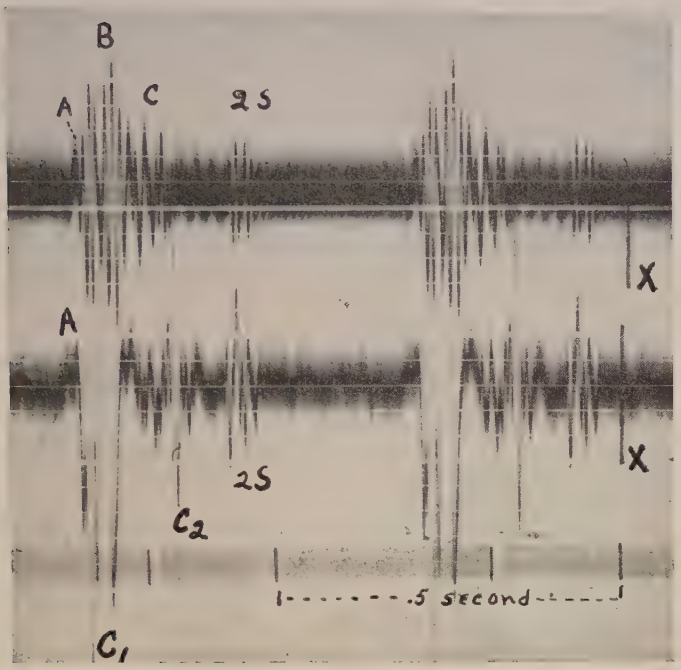

FIG. 61.—Sound vibrations recorded directly from heart. Upper curve, ventricular sound showing *A*, preliminary vibrations; *B*, main vibrations; *C*, final vibrations. Lower curve showing in first sound *A*, preliminary vibrations; C_1, first component; C_2, second component. Second sounds shown at 2*S*.

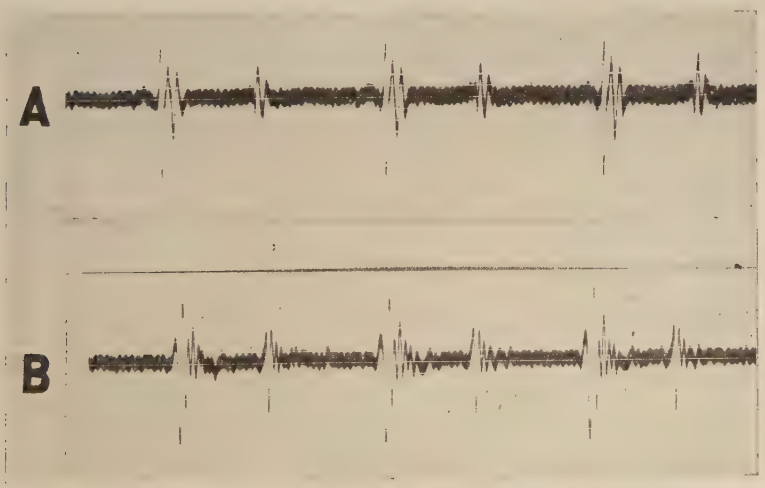

FIG. 62.—Two records of thoracic apex sounds in two normal adults showing characteristic records obtained. Second sound accentuated in lower record.

probably establish the correctness or fallacy of this suggestion; but unfortunately such phonocardiograms are, to the writer's knowledge, non-existent.

The study of phonocardiograms shows that heart sounds are not true musical sounds in the physical sense because they are made up of successive vibrations varying in frequency and amplitude. Physically, they are not different from murmurs.

Clinically, the heart sounds are valuable aids in determining the efficiency of the heart and circulation. Not only do the two sounds mark precisely the beginning of systole and diastole, but their intensity varies as the vigor of contraction and height of arterial blood pressure. The first sound vibrations increase in amplitude and number (i.e., the sound becomes louder and longer) when ventricular action is vigorous. They decrease in amplitude and certain vibrations may be entirely absent when the heart is depressed. The second sound both in the pulmonary artery and aorta increases in amplitude when the pressure at the beginning of diastole is higher and may be entirely absent when it is very low (personal observations). Laboratory experiments have, therefore, confirmed the clinical impression that the loudness of the first sound is, in a measure, an index of the dynamic efficiency of the ventricle and the second sound is a criterion of the height of arterial pressure at the beginning of diastole.

Anatomical Considerations of Physiological Importance.—In addition to the analysis of the direct functions of the circulation, there are certain anatomical changes during growth and development which are important in the final analysis of the physiology of the circulation.

Weight and Diameters of the Heart.—At birth the heart weighs between 20.6 and 23.6 gm. being, as a rule somewhat heavier in males. By the end of the first year its weight has practically doubled, averaging 44.5 gm. After that, it increases less rapidly, as indicated in the following table:

WEIGHT OF HEART AT DIFFERENT AGES (GOODMAN)

Years	Grams
1.0	20.6–23.6
2.0	44.5
3.0	60.2
5.5	72.8
10.0	122.6
17.0	233.7

At birth, the weight of the heart constitutes 0.76 per cent. of the body-weight, but, owing to the greater muscular and osseous development, the rate of growth no longer remains proportional to that of the rest of the body; consequently, in adults, the heart equals 0.46 per cent. of the body-weight (McMurrich[45]). As the weight of the heart increases during development, concomitant changes in its diameters

as well as in the thickness of the ventricular wall occur. At birth, the musculature of the two ventricles is equally developed. Anatomical studies (Müller[49]) as well as electrocardiograms indicate that by the second or third month the left ventricle has begun to increase in size and that by the sixth month the musculature of the right and left ventricles are related as in the adult. At birth, their capacity equals about 23 c.c. This has increased by the seventh year to 100 c.c.; by the tenth year to 140 c.c. and by the fifteenth year to 150 c.c., reaching in adults 260 c.c. (Goodman[20] and Hochsinger[30]).

The Position of the Heart.—The heart originally develops in the cervical region, but, as the diaphragm moves downward in the course of prenatal development, it draws the heart and pericardium with it into the thoracic cavity At birth and during the first three or four years of life, the diaphragm still remains relatively high and, in consequence, the axis is more horizontal. The apex is therefore situated higher and farther to the left than in adults. Although many variations occur, it may be said that the average apex is located in the fourth intercostal space, about 1 cm. or more to the left of the nipple line. As the diaphragm, due to the upright position and changes in the thorax, gradually descends in relation to the bony thorax, the heart rotates about the basal vessels as an axis and becomes more vertical. This displaces the apex to the fifth intercostal space at the nipple line (Keating and Edwards,[35] Wassilewski,[64] Wilson,[71] etc.).

The heart is a very movable organ in children, altering its position and axis readily with changes in body posture and in the level of the diaphragm. The right border may thus change from the left sternal border to 2 cm. to the right border of the sterum when the patient changes from the left lateral to the right lateral position (Butler[6]). In addition to these alterations with posture and at different ages, it should be borne in mind that the heart changes its thoracic position during every cardiac cycle and with every phase of respiration.

During each systole the base descends, the apex rotates anteriorly and, in doing so, moves downward to a slight extent. This slight downward movement is evidently the cause of the apex impact felt through the intercostal spaces. During every inspiration, the pericardium and large vessels passing through the diaphragm are pulled upon. This tends to pull the entire heart downward and, in addition, tends to rotate the apex clockwise so that it moves farther inward and downward during this respiratory phase. All of these influences tending to cause a change in the position of the heart are operative to a much greater extent in children than in adults and should be borne in mind in the percussion of the cardiac areas. For further details concerning the physical examination of the heart, the reader is referred to the chapter on physical diagnosis.

The thoracic vessels progressively increase in size from infancy to puberty. These variations in the size of the pulmonary vessels and aorta are briefly indicated in the following table given after Beneke and Vierordt.[62]

Age	Body length, cm.	Pulmonary artery, mm.	Aorta, descending, mm.	Aorta, thoracic, mm.
Birth.....	49.00	23.5	18	14.25
1.5–2	77.00	37.0	34	22.60
6.0–7	109.25	43.0	39	28.00
14.5–15	150.00	51.0	48	34.00
24.0–31	161.25	64.0	60	43.00

In this connection emphasis is usually laid upon the fact that while the ventricular walls and the capacity of the heart increase rapidly during childhood, the large vessels and arterial ostia increase very much less in diameter. This increases the resistance to the blood flow from the ventricle materially and increases the force required for the expulsion of the same proportional quantity of blood (Hochsinger[30]).

During childhood important changes gradually take place in the histological structure of the blood vessels. In the aorta and pulmonary arteries the intima develops more than the media. In the medium sized vessels, the media undergoes the chief thickening. Up to the age of eight and one-half years, the intima of the brachial and femoral arteries is equal, but by the time adult life is reached the intima is thicker in the femoral artery. The adventitia of the brachial and femoral arteries exceeds in thickness the media at all ages; for the aorta and pulmonary arteries, this is not true post-natally (Dobrowlski[12]).

The Circulation at Different Ages.—Having reviewed the principles of the circulation as established by experimental work, and the possible avenues by which data in regard to the circulation in infancy and childhood can be obtained, it remains to formulate, on the basis of such knowledge as we possess, a concrete physiological picture of the circulation at different ages. For this purpose we may divide the period of childhood arbitrarily into four intervals, understanding, of course, that all changes occur gradually and are not sharply demarcated at any age limit.

Circulation during Infancy.—(Birth to two and one-half years.) At birth, the work of maintaining the arterial circulation is suddenly shifted from the joint action of two ventricles which have been equally developed to that of the left alone. Owing to the fact that the reserve power of the left ventricle is immediately called into full use, this chamber is at once capable of accomplishing the work thus suddenly thrown upon it. On account of this greater functional activity, the stimulus to increased growth is supplied so that by the sixth month, the left ventricle has undergone greater development than the right or, viewed from another aspect, has undergone a "physiological hypertrophy" which it continues to maintain throughout life.

During no other period of life is the heart beat so truly a purely intrinsic affair as during infancy. No extracardiac control of any importance has developed. The rate therefore is always rapid, rarely falling below 110. The vagi fibers, as well as the cardio-inhibitory center in the medulla, are irritable, however, and when stimulated during infections or by an increase in intracranial pressure, may cause a slowing of the heart.

It is impossible to picture precisely the dynamic mechanism of the heart at this age, as so many factors are unknown. In the first place, we have not sufficient evidence that the venous pressure during this period is high enough to adequately fill the ventricle early in diastole. The blood volume is apparently small in relation to the body-weight and the hemoglobin percentage and the red blood cell count are less than in adults. In the second place, the elastic tissue which in the adult heart aids considerably in the rapid return of the ventricles to a relaxed condition is not present to any great extent. It is therefore quite possible though, of course, not proven that in early life the ventricles fill more slowly during diastole and are assisted perhaps more materially by auricular systole than they are in later years.

As to the quantity discharged per beat (systolic discharge) or per minute (minute volume), no direct estimates for this age have been made. It is therefore necessary to approximate these volumes by calculation. At birth, each ventricle has a capacity of about 12 c.c. Cardiometric experiments on dogs' hearts of equivalent weight indicate that the ventricle does not empty itself completely but that approximately 4 c.c. is ejected when the heart beats at the rates of 110 to 120 per minute. The minute volume thus becomes 440 to 480 c.c. If we roughly estimate that, as in adults, 8.8 per cent. of the body-weight represents blood (Keith, Geraghty, Rowntree[37]), then a child weighing three kilograms would have at birth 264 c.c. It is evident that it requires about one-half a minute or actually 66 beats to pump a quantity of blood equivalent to the entire amount in the body. Calculation, on this basis shows that 100 gm. of body substances receives 16 c.c. per minute, a much larger flow than is found in adults in whom the flow per 100 gm. has been actually estimated at 6.12 c.c. per minute.

The small systolic discharge can readily be accommodated in the aorta which at birth has a diameter of 18 mm. Partly for this reason, and partly because the left ventricle has not yet relatively increased to adult proportions, the pressure during systole is elevated only 18 to 20 mm. above the diastolic. This figure represents the pulse pressure. As the musculature of the left heart, as well as the size of its cavity, progressively increases during the first year, the output also gradually increases and the pulse pressure, in consequence, is increased from 20 to 34 mm.

Circulation during Early Childhood.—We may be fairly certain of the statement that during this period the venous pressure has increased sufficiently to adequately fill the ventricles early in relaxation. A distinct positive venous pulse is present indicating

a filling pressure considerably above the negative intrathoracic pressure. The fact that the first sound is clear and loud may further be taken as an indication that an effective pressure is present. The dynamics of the heart beat under such conditions are chiefly determined by the heart rate. During ventricular systole, blood accumulates in the auricles and large veins in sufficient quantity so that at the onset of diastole, blood flows rapidly into the ventricle. While this inflow is still taking place auricular systole supervenes, causing an additional though small filling increment, at the same time elevating the intraventricular pressure. As long as the heart rate remains above 80, which is usual during these years, no interval of diastasis is present, the ventricles being either in the act of filling or discharging during the entire cardiac cycle. The slight increase in the diastolic interval, however, together with the constantly increasing venous pressure and enlarging capacity of the ventricular chambers results in a larger ejection. The left ventricle of a dog's heart of weight equivalent to that of a child's of three years (50 to 60 gm.) ejects from 13 to 25 c.c. of blood with each beat. Taking 20 c.c. as the average estimated output of the child's heart at this age, and the rate as roughly 100 per minute, the minute output becomes 2000 c.c. per minute or over four times that at birth. That the minute volume actually increases after the fashion calculated from animal analogy is attested by the increase in the product of the pulse pressure and the heart rate. The greater systolic discharge makes itself evident in a higher systolic pressure and as the diastolic pressure is elevated very little, the pulse pressure increases correspondingly. This is evident in the following comparisons.

Age	Systolic pressure	Diastolic pressure	Pulse pressure	Heart rate	Pulse pressure × heart rate
Birth	68.0	50.0	18.0	110	2160
4 yr	92.6	61.7	30.9	100	3090

The Circulation during the Period of School Age.—At this time of life important changes have already been completed which insure a mechanism of the heart beat not essentially different from that in adults. In consequence of the relatively greater development of the left ventricle together with the descent of the diaphragm, the heart occupies a more vertical position so that the apex beat occurs nearer the median line and an interspace lower than in early childhood. Elastic tissue capable of assisting a rapid and full relaxation in diastole has developed in connection with the muscular syncitium in both ventricles. The vagus nerve has gained a functional control over the heart, thereby progressively decreasing its rate which reaches 84 or less by the end of this period. The

latter two features inaugurate essential dynamic changes in the heart beat. Now, for the first time, a rapid relaxation and a maximal filling are possible early in diastole, for the period of filling is unabridged by the next systole—in fact, a period of diastasis actually occurs before auricular contraction supervenes. All these factors combine to increase the systolic discharge and the height to which intraventricular pressure can be raised. These changes are evident both in changes of the systolic and diastolic arterial pressures and in an altered character of the sounds. According to dynamic principles, the increased systolic discharge combined with a slower heart rate should cause a larger pulse pressure but lower systolic and diastolic pressures. Actual observations at these ages show, however, that the diastolic pressure is unaltered while the systolic pressure is actually increased. This can only mean that important compensatory changes in the peripheral circulation have taken place. Whether this is due to a physiological increase of the vasomotor tone or merely to the increased resistance offered by the constantly growing vascular system or changing elastic components of the blood vessels cannot be determined.

There can be no doubt that the minute volume discharged by the heart increases markedly, but no estimate can even approximately be made either from the analogy of animal experiments or from calculation of the products of pulse pressure and heart rate because the peripheral pressure has varied so greatly.

When the tonic vagus activity develops, it apparently often acquires a variable and rhythmic variation. This produces not only an arrhythmic condition of the pulse but also affects the dynamic action of the heart in such a way that short and long cycles with small and large outputs intermingle. The effect is to produce an elevation of the systolic pressures and a decrease of the diastolic pressures during the slow beats; and a decrease in systolic and increase in diastolic pressure during the more rapid beats. Both systolic and diastolic pressures are therefore variable and may change as much as from 10 to 15 mm. of mercury. This may be noticeable in blood pressure determinations during these years. Thus, if the pressure within the constricting cuff is gradually released, an occasional sound may pass through the cuff and not until the instrument reads from 10 to 18 mm. lower are all sounds allowed to pass. Properly speaking, we should read the maximal and minimal systolic and diastolic pressures in such cases. This fact has apparently not been sufficiently considered in blood pressure determinations when cardiac regularity is frequently present and our tables for these ages must be regarded as only approximate.

With the increased muscular development together with greater filling and ejection concomitant with a slow heart, the first sound becomes composed of more vibrations at the apex and acquires a greater muscular component. The writer suggests that it is very possible that with the more vigorous ejection of blood into the aorta,

a second component is added to the first sound which manifests itself on auscultation as an impurity or murmur.

Circulation during the Period of Adolescence—(12 to 16 Years).—During this period, the dynamics of the circulation do not differ essentially from those previously described. By the sixteenth year, the heart has adopted its adult rhythm and is susceptible to the same extracardiac influences. Phasic arrhythmia may still be present and extrasystoles both of the auricle and ventricle are common. In size and volume the heart is only slightly below the adult stage. Its ejection and the condition of the peripheral circulation, judging from the blood pressure, are similar to those in young adults.

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CHAPTER LXIX

PHYSICAL EXAMINATION OF THE HEART IN NORMAL CHILDREN

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Before the first congress of Pediatrists in 1883 (The Infantile Therapeutics Congress of Berlin) practically all data collected on the heart of the child was incidental and consequential to the study of the heart of the adult. During the next 10 years, the specialty of pediatrics became permanently established. A large amount of clinical research was done on the normal heart of the child, with especial reference to the anatomy and physiology, as differing from that of the adult. The majority of pediatric text-books make little or no mention of this subject, and other texts have copied the data of the earlier authors, with no attempt to corroborate or refute their authenticity by means of the more accurate and precise methods for investigation.

The great and many differences between the heart of the child and that of the adult are not sufficiently emphasized in the class room. Most instructors in pediatrics teach students the same principles of cardiography as are taught in internal medicine. The undergraduate is given only a general and superficial idea of the heart of the child. When he begins the practice of medicine, he is improperly and insufficiently prepared to diagnose and treat the heart diseases of children.

The following chapter upon the Physical Examination of the Heart of the Normal Child, has been written primarily with the point in view of emphasizing and re-emphasizing the peculiarities and individualities of the growing heart as they are related to clinical diagnosis. The substance of the following pages is based to a limited extent upon original work, but largely upon a carefully attempted comparison and analysis of all reliable writings on this subject. The opinions given and the conclusions drawn are an attempt to give to the reader, in a concentrated study, the result of all obtainable research on this subject.

Anatomy and Physiology of the Heart of the Child.—A complete knowledge of the peculiarities of the anatomy and physiology of the heart of the child at different periods is of great aid in physical diagnosis. The anatomical data given to us on this subject, with the exception of the more recent works of Müller, Gundobin, and a chapter in this system by Scammon, is subject to great criticism. Much of the material used for investigation was pathological, and the reader does not know whether or not the hearts in question were normal. There was no uniformity of technique in the dissection and weighing of

the hearts; some of the hearts being weighed with the pericardial fat, others without, some with the large vessels, others without.

At birth the heart is relatively larger than at any other period of life. At this time it is about 20 to 24 gm. in weight, which is about 0.86 per cent. of the total bodyweight, as compared to about 0.52 per cent. in later life. It doubles its weight at about the eighth month, triples it at about the second year, quadruples itself at about the fifth year. It is 11 times as heavy at the sixteenth year as it is at birth.

During the first year of life the heart undergoes a tremendous physiological hypertrophy, which involves all parts and extends unequally in all directions. The growth of the heart is more or less dependent upon the general body growth. In the first few years the growth of all tissues especially those of the organs is very rapid and the heart necessarily shares in this development. At birth, the length and the width are about equal but after this period the length becomes greater than the width. By six years the length has doubled but the width is not doubled until about the ninth year.

During the first four years the length is about 5.1 cm. as compared to the width which is about 5.8 cm. Between five and nine years, the ratio between the length and the width is as 6.5 to 7.0. Between one and 15 years, the length is 7 and the width is 7.12 cm.

The increase of the weight of the heart is due largely to the increase of the ventricles. At birth, there is practically no difference in thickness or weight between the right and left ventricles. However, shortly after birth the left ventricle is called upon to do more work than the right, and since the size and strength of the different parts of the heart are indices of their function, the left becomes preponderant over the right.

At birth, the wall of the right ventricle is about 3 to 4 cm. thick, and the left is about 4 to 4.5 cm. thick. At the end of the first month, the left ventricle is slightly thicker than the right. At the end of the first year the left ventricle is twice as thick as the right and at puberty it is three times the thickness of the right.

In newborns the ventricles are about four times greater in size than the auricles, and in later childhood about six times greater. The right auricle is slightly predominant over the left, but in about two months and during the first year they are about equal in size and thickness. Following the first year, the right auricle grows faster than the left and during the remainder of childhood, the right is about 5.5 per cent. greater than the left auricle.

During the first few years the heart undergoes the greatest increase in volume. From a capacity of about 22 cm. at birth, it changes to 44 cm. at two years. By five years it has grown to about 90 cm. and at puberty it has a capacity of about 140 cm. For a detailed exposition of this subject the reader is referred to the chapter on the "Anatomy of the Child," by Scammon in Volume I of this System.

The Form and Development of the Thorax.—The growth and development of the thorax of a child are of peculiar interest, not only

anatomically, but in their influence upon the physical diagnosis of the heart.

In the newborn, the transverse and the sternovertebral diameter of the thorax are equal, each being 8 cm. The transverse diameter outgrows the sternovertebral very rapidly, so that by six years it is 18 cm., while the latter is 14 cm. At about 10 to 12 years, the transverse is 20 cm., and the sternovertebral is 14½ cm. The upper-edge of the sternum of the newborn is on the level with the first dorsal vertebra, while in the adult it is on the level with the lower part of the first dorsal vertebra. At birth, the central tendon of the diaphragm, which is the lower limit of the thorax, is at the level of the discs of the eighth or ninth thoracic vertebra, one space higher than it is in the adult. The diameter of the chest on the level with the upper end of the sternum is smallest at birth, while that on the level with the eighth rib is the largest. The smallest diameter makes the greatest increase.

The relationship between the transverse and the posterior diameters found in the adult is reached at about 10 years.

In the process of growth, or as the result of disease, the heart may be displaced to such an extent, on account of the consequent changes of the chest, that both relative and deep dulness may be altered materially. A change in the shape of the thorax from the normal conical to the quadrangular and triangular may cause a marked change in the area of the heart. An asymmetrical chest may be caused by pleuritic adhesions, which pull the heart over to one side, or may be due to a scoliosis, which may be physiologic or associated with infantile paralysis. Under such circumstances, hypertrophy may be diagnosed when the heart is not actually enlarged. Rachitis is rather a common cause of deformities of the chest and therefore, in the child, of displacement of the heart.

In congenital heart lesions, there is sooner or later a bulging of the precordium. The flat, narrow, long chest with wide intercostal spaces is frequently found in neuropathic asthenic children. This condition causes a drop in position of the entire heart, to the extent of one or even two spaces lower than the normal.

Position of the Heart.—The position of the heart can be determined by post-mortem dissection, by percussion of the borders and the localization of the apex beat, and by Roentgen-ray examination. The very early attempts to establish a normal standard for the position of the heart of the child at different periods were made by percussion of the heart and determination of the apex beat, or by anatomical observations, or by a combination of both methods. The data obtained from anatomical observations cannot be applied accurately to physical diagnosis, because in the young, especially in the infant, the liver, after death, pulls down the diaphragm and with it the thoracic contents. This causes a lowering of the entire heart at least one space and sometimes two spaces. An insufficiency of mate-

rial has precluded criticism-proof investigations of all the ages of childhood from which to draw conclusions.

The determination of the position of the heart by palpation and percussion is also inadequate mainly because the method is not sufficiently objective to give constant results. Of all three methods the *x*-ray examination is the most adequate, but also in itself alone has some objections. At birth, it is practically impossible to get a clear outline of the baby's heart with the *x*-ray, and during infancy there is not enough ossification to give landmarks on the anterior wall of the chest.

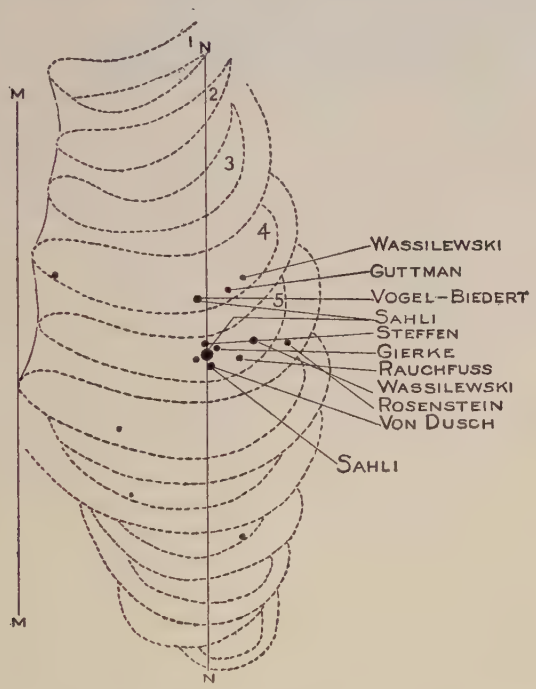

FIG. 63.—Position of apex beat in normal children. *M*, midsternal line; *N*, nipple line. Distance of midsternal line to nipple line, 6.5 cm.

In general, the heart of the child lies higher in the thorax than does that of the adult. It is also more horizontal and the apex beat is farther out. As the child grows older the heart falls downward and inward, and at about the seventh year of life assumes the adult topography. In the newborn the upper border of the heart is about on the level with the second intercostal space (Fig. 63). The auricles are beneath the second space and the upper part of the third rib. The right auricle lies directly in front of the left auricle, but does not touch the chest wall. The foramen ovale lies in an almost horizontal plane and not vertically as has been supposed. The left auricle occupies the extreme back of the heart, and extends throughout the entire

width of the base of the heart. It is bounded in front by the right auricle and the left ventricle, behind by the thoracic aorta and esophagus, and above by the right pulmonary artery and the left bronchus. The heart is directly in front of the vertebral column, and a posterior coronal section shows the upper border on the level with the fourth and fifth vertebra and the lower border on the level with the eighth or ninth thoracic vertebra.

The right ventricle lies beneath the sternum and a little to the left of it. In infancy, it alone comes in contact with the anterior chest wall. Its lower border is about on a level with the sixth rib in front. It is bounded by two structures, the left ventricle below and the root of the aorta above. The left ventricle lies more to the left than the right ventricle and underneath the third and fourth intercostal spaces. It is bounded by the left auricle behind, and by the right ventricle in front.

The valves lie closer to one another than in the adult in an area of about 1 square cm. The mitral valve is at the third space slightly to the left of the sternum. The tricuspid, lying beneath the sternum a little lower than the mitral, is practically vertical and opens to the left. The mitral and tricuspid orifices lie in planes which are almost at right angles to each other. The pulmonary orifices are opposite the second left intercostal space, still a little lower, and the aortic is slightly oblique to and a little lower than the pulmonary.

The change from the infantile position to the adult one is very gradual, but as nearly as can be estimated the adult topography is established at about the seventh year, when the heart apex beat can be seen and felt in the fifth interspace inside of the mammillary line.

Position of the Apex Beat, Importance and Significance.—In the normal adult, the apex is constant and fixed. In the child it changes with development, and is found in different positions at different periods. In general, by localizing the apex beat, the left border of the heart can be easily and quiet accurately determined if one bears in mind the anatomical peculiarities of the different periods, the shape and size of the thorax, the body-weight and length of the child.

The apex beat is not synonymous with the heart beat. The heart beat is the visible and palpable impact of the heart against the thorax, whereas the apex beat is that part confined to the neighborhood of the apex. To locate the apex beat, one places the palm of the hand over the precordium with the fingers pointed towards the axilla, using the finger tips to localize the apex beat.

The actual apex beat in the normal child is circumscribed to one space in the infant, about 2 cm. in diameter, and to one or two spaces in the older child. In the newborn it is rarely visible or palpable, while in the older child, it may be either seen or felt or both. Usually there is no difficulty in localizing it in the older child.

The middle point of the apex beat usually corresponds to the apex of the heart, that is, to that part of the deep cardiac dullness which lies farthest to the left or more often a little within. The

outer part of the apex is dulled by the overlapping lung, so that the maximum point of the beat is really a little within the true apex.

In the adult, the apex beat is formed only by the left ventricle, but in the child, especially in the infant, the apex beat is made up of about one-half of the right ventricle. This is due to the fact that the right ventricle, at birth, is as large as the left and remains relatively preponderant for at least six months.

The intensity of the apex beat varies in different children and at different ages in the same child. The thickness of the walls of the thorax and whether or not the beat happens to be behind a rib are all factors which influence the intensity. The change of the apex beat is greatly influenced by the change of position of the body. It moves

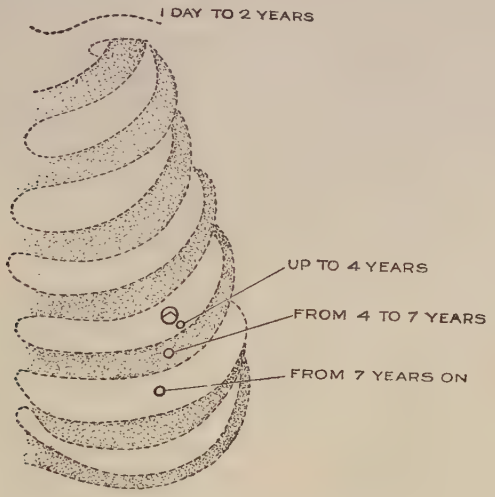

FIG. 64.—Position of apex beat of the normal heart at three different periods of childhood. (From Starck.)

as much as 2 cm. to the left or to the right respectively, with a change in the position of the body. If the child is lying on the right side, the apex beat may be entirely impalpable on account of the overlying lung. Pushing the body forward will sometimes make an invisible or impalpable apex beat visible or palpable. Deep expiration may bring out the beat more prominently because the lungs become retracted. Psychic or physical stimulation to cardiac activity usually intensifies and diffuses the apex beat.

In Fig. 63 an attempt is made to compare the results of various observations on the normal positions of the apex beat during entire childhood. In a series of 16 investigations of this subject, the results of 10 are here recorded. The difference of opinion is mainly due to the difference in ages. This is to a large extent eliminated in Fig. 64 which shows the positions of apex beat at three different periods of childhood. A few of the observers failed to take into consideration the

racial peculiarities of the children, others included abnormal cases in which there may have been incomplete or improper development of the thorax. The works of Stark, Sahli and Gierke are the most accurate.

Figure 64 shows the average position of the apex beat at three different periods, taking the work of Stark as a basis. In the first year, the apex beat, if it is visible or palpable, is always outside the nipple line from ½ to 1½ cm. In the majority of cases, about 88 per cent., up to four years it lies outside the nipple line, but rarely lies there after seven years. It usually lies within the nipple line by the ninth year, and is always found within the nipple line from the twelfth year on.

The apex beat during the first year almost always lies in the fourth space, and from then on it gradually becomes lower so that during the second year it is usually in the fourth space, rarely in the fifth. From the third to sixth year it lies quite often in the fifth space, and from the seventh year on most often in the fifth space.

It is very rarely found in the sixth space in a normal thorax, except in the congenitally asthenic type of chest, where a drop heart is found, or where there is a general visceroptosis.

From the foregoing it can be seen how important it is to bear in mind the different ages, in order to recognize what is the normal position of the apex beat.

In general it can be said that in the first half of childhood the apex beat lies in the fourth, or fourth and fifth, and in the second half of childhood it lies most often in the fifth space. Up to three years it is never more than 2 cm. outside of the nipple line and after that, never more than 1 cm. These can be used as normal limits. If the apex beat is outside of these limits, one must always be suspicious of an abnormal heart, providing that the nipple is not in an abnormal position.

Percussion.—The determination of the size of the normal heart of a child, obtained at different periods, by means of percussion, is the cause of much dispute. Percussion as a method of physical diagnosis is not sufficiently objective. It involves the personal equation of the examiner, what he considers the first change of tone, the conditions under which the examinations are made and the technique he employs in his percussion.

The results obtained from percussion are affected by many varying factors in a growing child, *viz.*, the position of the child while being examined, the size and shape of the thorax, the vibrations of the walls of the thorax, the overlying lungs, the skeletal characteristics of different children of the same ages, and the difference of children of the same age in body-weight and in body length. It is because of these physical individualities in children of the same period, and because of the lack of uniformity in the method employed by different investigators, that percussion *per se* is an inadequate and inaccurate means for formulating the standard position and size of the hearts of children

of different ages. However, with the aid of the x-ray and anatomical dissections there is sufficient accurate data which can be used as a clinical guide for the normal.

The technic to be employed in percussion is especially important. It is always best to percuss the back first. One should attempt to carry out the examination without the child being aware that anything unusual is being done. A very delicate stroke is necessary because in

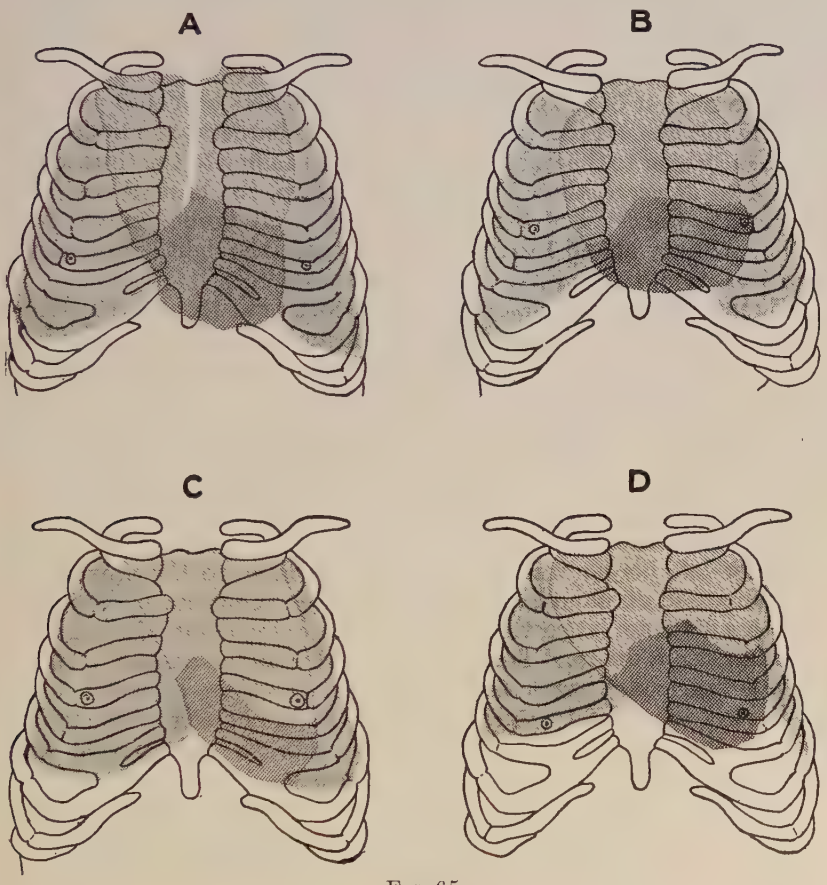

FIG. 65.

the young, on account of the thinness of the chest walls, the tone produced is very easily modified by the surrounding tissues.

In the adult absolute dullness may give quite accurate results, but in the child it is practically impossible to elicit accurately the uncovered portion of the heart.

In newborns the author has attempted many times to compare his results from percussion, by making three or four examinations at one sitting, but there has been too great a variance to justify recording.

Figure 65 (*A* to *D*) represents the anatomical size and position of the hearts of four different normal newborns of about the same weight. It can be seen from these figures how absurd it would be to attempt to percuss the uncovered portion of the heart. Because of the thymus above, which is different in various children, and because of the overlapping lung on either side, which in different children represents different stages of respiration, and because of the relation of the liver to the heart, the heart borders cannot be percussed with any constancy.

The majority of observers consider that the absolute dullness in the nursling is bounded above by the third rib; that the right border is just to the left of the sternum; and that the left border is precisely at the nipple line. From two to four years the borders are a little lower and slightly over to the right, the upper border falling to the third space. From 4 to 12 years, there is still another drop, the base of the heart descends to the level of the fourth rib; the left border moves from the mammillary line to 1 to 2 cm. within it, and the right border moves from 1 to 2 cm. to the right of the mid-sternal line.

Figure 66 shows the difference in size and position of the absolute dullness as obtained by the most accurate observers. Steffens claims that he could differentiate the position of the auricle from the ventricle, but this is denied by all the others. He found the area of absolute dullness a triangle with the apex directed upwards and the base corresponding with the lower border of the heart.

The diameter of the triangle is from 3½ to 4 cm., slightly longer than wide. Rauchfuss disagrees with Steffens. He found the absolute dullness larger and less conical in shape and slightly lower; the outer left border was about 1½ cm. nearer to the nipple line. Weil percussed an almost quadrangular shape about one space higher up with a diameter larger than the other figure by about ½ square cm. Sahli has still a different figure. He found that the area of absolute dullness assumed a right angled triangle, the apex of which is on the level of the second space, the base is at the bottom of the fourth rib and the right border runs parallel with the left sternal line. This figure is higher than any of the others.

The only conclusion that can be drawn from a comparison of all the figures obtained by this group of clinicians is that the absolute dullness is not entirely adequate for use in clinical diagnosis.

Relative Dullness.—As shown in Fig. 66, the results obtained from the percussion of relative dullness in comparison with each other differ, although not so much as the results obtained from that of absolute dullness. Steffen found that the superficial area of dullness is an equilateral triangle with the hypotenuse forming the left border. This figure is more nearly like that of a fluoroscopic shadow of a heart than that obtained by the others. The apex is found in the fifth space and the top of the base on a level with the lower edge of the third rib. The lower border is represented by a slightly curved line from the apex to the lower point of the right border.

Rauchfuss found a larger area of dullness especially to the left. The left border starts at the bottom of the second rib at the left edge of the sternum and curving convexly cuts the parasternal line at the third rib, the nipple line at the fourth rib, and forms the apex at the sixth rib, 1 to 2 cm. outside of the nipple line. The right border is a convex line curving 2 cm. to the right of the mid-sternal line, and ending at the right of the sternum on a level with the upper part of the sixth rib. The lower border joins the lower points of both right

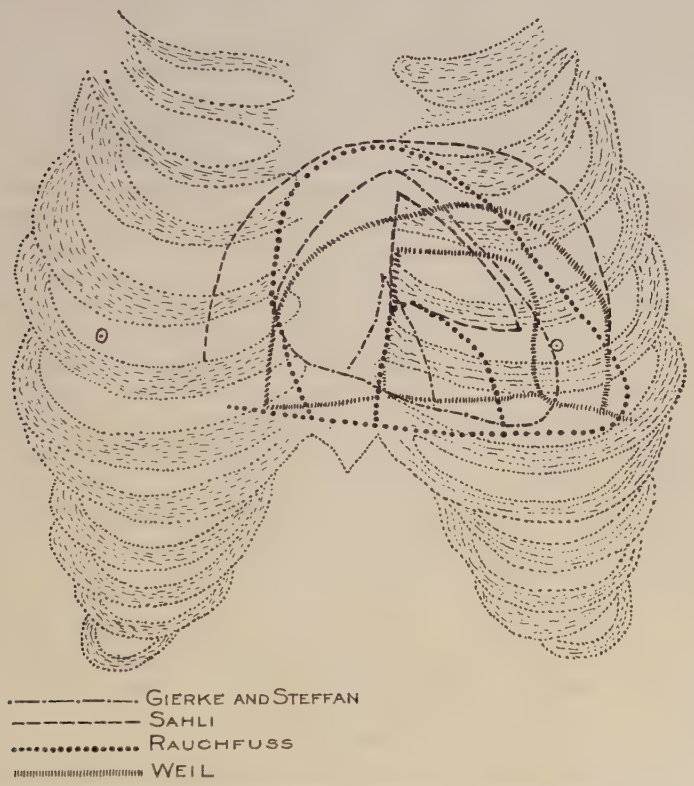

FIG. 66.—Distance of mammilla from the middle line to the left is 5.5 cm. (absolute diet, 6.2). Distance of mammilla from the middle line to the right is 6.4 cm. (absolute diet, 7.2).

and left borders. This figure corresponds more closely to the anatomic position and shape of the heart.

The upper border of Weil's figure is on the level with the second space, reaches beyond the nipple line to the left and on the right side forms a convex curve, of which the widest point is on the level with the fourth rib at the edge of the right border of the sternum.

Sahli found the relative dullness higher than any other investigator. His figure resembles a stiff hat with the top as the base of the heart. It does not resemble at all the *x*-ray shape of the heart.

He admits that the results were not sufficiently constant to justify his establishing a normal standard for all ages of childhood. He found a change in some children at six years and again, in others, the infantile relationships still obtained at the age of 12. His figure is wider because he obtained his right and left borders at the very slightest noticeable change in tone.

The work of Von Stark, in which he groups the normal size and position of the heart of the child in three different types, is probably the most reliable classification in use. His Type I corresponds more closely to that of Sahli. Types II and III resemble more nearly that of Weil.

Figure 64, Type I, represents the average area of dullness obtained by a percussion from birth to the second year of life. The highest point of this figure is on the level with the sternal end of the second left rib. Von Stark does not attempt to localize the border of the base of the heart at this period, because of the presence of the thymus. The left border of the heart runs in a convex curve, its farthest point out being 2 to 2½ cm. from the left nipple line, on the level with the upper part of the fifth rib. The right border also forms a convex curve to the right from the second right space, to the upper border of the fifth rib. He believes that in only a few instances can the lower border of the heart be accurately determined. At this age, the widest diameter on the level with the nipples is about 6.6 to 8 cm. Of that 5 to 5.5 cm. lie on the left of the mid-sternal line, and about 1.5 to 2.5 cm. to the right. In the first few weeks of life, he claims that the right side is proportionately wider than towards the end of the first year on account of the relative preponderance to the right ventricle. This is true anatomically, but the author has failed to confirm his opinion by percussion.

Type II covers the period from two to six years. During this time there is a change mainly in the upper part of the heart and in the lower left border including part of the apex. The base of the heart lies usually in the second interspace, the left border crosses the third left rib at the parasternal line, the fourth rib in the nipple line, and the fifth rib about 1 cm. outside of the nipple. The right border does not curve as much as in Type I. There is a very slight change in shape from the first type, the right upper curve being less accentuated as the child grows. The heart at this period averages about 10 cm. in its widest diameter, about 2.5 cm. to the right and about 7.5 to the left.

Type III—from 6 to 12 years, the heart is lower. The apex beat is on or within the nipple line, and the lower border is on the level with the fifth space on the upper part of the sixth rib. The left border crosses the parasternal line at about the lower border of the third rib, the nipple line at the fourth rib, and then turning slightly inward reaches the lower heart border at about the sixth rib. The right border intersects the right sternal border at the fourth rib, then runs parallel to the sternum and ends at about the lower part or the fifth

space. The greatest width at this age is about 11 cm., 3 to the right and about 8 cm. to the left.

In conclusion, the author wishes to emphasize that the figures given above as normal, for different periods are an approximate and elastic index of the actual size of the heart, and thus should be used accordingly. In the adult, the left border is always within the nipple line, whereas in the younger child it is usually outside of this line. In the adult, the upper part of the sternum is always clear; in the period of infancy, it may be impaired on account of the thymus. The deep and superficial dullness are obtained with great difficulty and variable results in the child, and it is practically impossible to establish an inflexible rule through percussion regarding the change from the infantile to the adult type. In general 2 cm. more or less than the above figures, given as normal averages, can be allowed for a normal variance. Any increase in size to the left indicates an enlargement of the left ventricle. An increase to the left and upward indicates enlargement of the left auricle mainly, and to a lesser extent the left ventricle. If percussion shows increase to the left and downward, the left and right ventricles are involved, and lastly, enlargement to the right involves mainly the right auricle and only slightly the right ventricle.

Auscultation.—Auscultation is the most useful and reliable of all clinical methods in the diagnosis of heart diseases of children. To use the stethoscope is the easiest, the most readily applied and also the most objective means of physical examination. Generally speaking, this means is more difficult in the child than in the adult on account of the lack of coöperation between the patient and the examiner. On the other hand, there is a distinct advantage in the fact that the heart of the child reacts to disease more simply than the heart of the adult thereby rendering the physical examination less complicated.

The binaural stethoscope is the most popular in this country. The best instrument is that which has a small bell about ½ in. in diameter which is covered with soft rubber.

In auscultation the baby should be held naturally in the mother's lap and in a sitting position, unless it is too sick. It is better to listen to the back first. During the examination if the baby is not quiet, the attention of the patient should be diverted by a light or a sound. The success of an auscultation depends as much upon the patience and the resourcefulness of the examiner, as upon his skill in physical diagnosis. In the newborn, the heart rate and the respirations are so rapid that it is very difficult, especially if the baby cries, to hear the heart sounds clearly. However, usually during the forced apnea, one may hear several cycles with sufficient distinctness to determine whether or not they are normal. Sometimes it may be possible to hear the sounds more clearly over the scapula than over the precordium, because of less interference from respiration. Just as in the adult, the physician should examine the apex, the middle of the

precordia, the lower part of the sternum, and over the two intercostal spaces on the right and left sides.

The rate, the rhythm, and the quality of the tones over all these areas should be noted. The patient should always be auscultated in both lying and sitting positions, both before and after exercise.

There are several anatomical and physiological reasons for the differences in the sounds of the child's heart and those of the adult. The first heart tone is caused mainly by the contraction of the left ventricle in its attempt to expel the blood into the arterial system, and the second sound by the closing of the semilunar valves. In general the first sound is louder throughout childhood than in the adult. Only in the first few weeks of life the sounds are weaker. The muscle mass of the child's heart is relatively larger than that of the adult, and since it is an accepted fact that the loudness of the heart tones depends largely upon the myocardium, the reasons for the differences in the tones are apparent.

Generally speaking, in the normal heart the sounds are loudest in the following order: First, at the apex, second, over the tricuspid, third, at the left second interspace (the second pulmonary sound), fourth, the first pulmonary, fifth, the second sound over the apex, sixth, the second note over the tricuspid, seventh, the first sound over the aortic (at the right of the second interspace), and eighth, the second sound over the aortic area. The degree and order of intensity of these sounds has been considered by some observers, especially by Hochsinger, as an important normal index. For all practical purposes, the first sound, at the apex, is usually the loudest, the succession from that being as follows: Second at the tricuspid, third at the pulmonary, fourth at the aortic area.

At birth the sounds are tic-tac in character as in the fetus. This usually disappears in a few days, although sometimes persisting for a week. At this time one cannot observe any difference in the tone of the sounds. At about the end of the second year, the first sound becomes booming, louder than the second, and remains so throughout all childhood, becoming more accentuated at about puberty. The sounds are usually louder in boys than in girls. They are louder in the standing posture than in the sitting, and louder in the sitting position than in the lying.

Pressure with the stethoscope changes the character of the tones considerably. The inhibitory mechanism controlling the heart is weaker in the child than in the adult, therefore the rate of the heart and the quality of the sounds is easily influenced. Crying, forced expiration, fever, however slight, cause accentuation of the sounds. In anemia and neurosis the sounds are often louder and give what is known as the "metallic clique." In chronic diseases of the lungs, which cause a disturbance of the pulmonary circulation, the pulmonary sounds are usually louder (except in pulmonary stenosis) over the tricuspid area and the apex. A slapping sound at the apex, as in the adult, is very suggestive of a mitral stenosis.

The second sound at the tricuspid area is also accentuated in all conditions where there is pulmonary or bronchial involvement as in pertussis of long standing, in asthma, and in congenital heart disease. The aortic sounds are very rarely accentuated in children. The aortic sounds are always weaker than the pulmonary tones in the normal heart, and since their accentuation depends upon an increase of peripheral blood pressure, and since diseases of blood vessels are extremely rare, accentuation of the aortic sounds is very rare. All the sounds are generally diminished in myocarditis and in the terminal stages of decompensation hearts.

The *gallop rhythm* is caused by an abnormally stimulated heart activity. It is physiologic in the newborn giving the tic-tac character to the tones. This phenomenon is rather frequent in children whenever the rate is greatly increased. It is of frequent occurrence in fevers. However, the true gallop rhythm, which is always indicative of myocardial involvement, is rare in children. It occurs most frequently in diphtheria, and in decompensated hearts with acute dilatation. It is always a grave omen under these circumstances.

Impurity, unevenness, roughness and splitting of the sounds, especially the first, are much more frequent in the child than in the adult. These are usually found in perfectly healthy children. They are too often diagnosed heart murmurs and treated as heart diseases.

Murmurs.—So much has been written on the matter of cardiac murmurs, so many classifications have been used, so many different explanations have been given for their causation, that after reading the literature one is bewildered in the attempt to apply all the various opinions and theories to physical diagnosis.

At birth and for the first few weeks, a heart murmur is quite common. It is practically always associated with a patent foramen ovale or a patent ductus arteriosus. With the physiological changes of the heart such murmurs generally disappear. Of a series of newborn babies at the University Hospital, in 34 per cent. murmurs could be heard during their stay in the hospital (10 days). During the first two years practically all murmurs are due to congenital heart lesions. Hochsinger contended up to 1915 that all murmurs were congenital during this period. Jacobi, Delabost, Schlieps, and others, however, have demonstrated authentic causes of acquired heart disease during infancy.

A non-pathological murmurs, unless it is caused by anemia, is unheard of during this period of life. From six years to puberty, murmurs become more frequent, the most common of which are the non-pathological. The most logical explanation for their frequency at this time is the fact that the heart is higher in the child, and the tension on the pulmonary vessels is relieved and renders the heart more dilatable.

Congenital Heart Murmurs.—As has been mentioned before, the vast majority of murmurs heard during the period of infancy are congenital in nature. They are often very loud, they may be musical

and harsh. The loudest murmurs one hears are always congenital. They may be heard all over the chest and back and even over the abdomen. The most common site for this class of murmurs is at the left of the sternum over the second and third intercostal spaces. This is usually the point of maximum intensity, from which they may be transmitted in all directions. Congenital heart murmurs are extremely variable on account of the involvement of more than one structure of the heart.

Acquired Endocardial Murmurs.—As in the adult these are the result of inflammation of the endocardium. They occur only rarely in infancy. They are usually a complication of sequela of one or more attacks of tonsillitis or rheumatism, although they may be the result of many other acute infections. Murmurs of acquired lesions are best heard at the apex and transmitted most often toward the axilla and the back. They are sometimes musical, rarely harsh, and although loud, not so loud as the congenital type. The systolic murmurs is by far the most common in acquired heart disease. It may or may not entirely replace the first sound at the apex. The diastolic murmur which is very rare in the child is always pathological and usually is a part of a double murmur.

Non-pathological Murmurs.—This form of murmur is much more frequent in the child than in the adult and has been a cause for much dispute and discussion. This group includes the accidental, the cardiopulmonary, the anemic, the functional, the compression, the atonic, and the inorganic murmurs. In a series of children examined by Zabler 64 per cent. were found to have murmurs which he considered were non-pathological. Hamill reported similar murmurs in 53 out of 80 children, Luthje in 623 out of 854 cases, and Zeyer in 352 out of 830. In drawing any conclusions from these figures it is of course important to know the ages of these children, and whether or not there were any other clinical signs of heart disease. It is also important to know how the investigators arrived at their conclusions, and what other methods of diagnosis besides auscultation were employed.

The author has selected for discussion 26 children from 6 to 12 years of age in whom he found what he considers non-pathological murmurs. He arrived at this conclusion by reason of the normal size and shape and position of the heart obtained by percussion, the absence of any signs of heart disease discoverable with the *x*-ray and the electrocardiograph. Only two of these cases had a hemoglobin of less than 80 per cent., so that in this series, although small, one could not classify these murmurs as *anemic*. Authors have reported very severe cases of anemia without any murmurs, and on the other hand children with normal hemoglobin may have marked murmurs, so that anemia and the presence of bruits may be only incidental.

Cardiopulmonary.—Of the above series only four presented characteristics which justified the diagnosis of cardiopulmonary murmurs. The murmurs were systolic and heard best at the left of

the sternum at about the third interspace rather than at the apex, as is claimed by some, and were markedly decreased and often absent upon holding the breath. The murmurs changed with the alteration of position but the author found no constancy in the change of the murmur with the alteration of position as is claimed by some observers. Such a murmur was diagnosed as cardiopulmonary on account of the absence of any signs of organic heart disease, and it was differentiated from all other non-pathological murmurs because of its being influenced by expiration.

Accidental Murmurs.—Of this series 15 cases may be considered as of the accidental types. There were absolutely no signs of heart disease and the *x*-ray shadows and the electrocardiograms were normal. Some were in so-called nervous children, but it could not be seen why nervousness should, as some think, cause this type of murmur. The murmurs were all systolic in time, soft, superficial, usually losing their intensity before the end of the first sound. In all cases the murmur was heard at the pulmonary second space; in about 50 per cent., the murmur was heard at both the pulmonary area and over the apex. In only three cases was it heard only at the apex. They were all well localized, only in one case was there any transmission into the axilla. The belief that these murmurs are heard best while the patient is lying and tend to disappear when in the erect position cannot be substantiated by the author's observations.

In the majority of cases the murmur is the least important sign in the differential diagnosis between organic and inorganic heart disease. After a careful survey of all the important literature on this subject, it would seem that a voluminous classification such as above mentioned is unnecessary and impractical. Such classification is of more academic interest than of diagnostic benefit. For all practical purposes it is sufficient to divide murmurs into organic and non-organic; if a murmur is not associated with enlargement of the heart, or other signs of heart disease, congenital or acquired, the murmur should not be given serious consideration, and the child should be advised to lead a normal life in every respect.

Venous Hums.—The venous murmur or hum is of very frequent occurrence in normal children. It is heard most frequently in the school age, rarely during infancy and it is influenced by position and by pressure with the stethoscope. There have been many various explanations for the causation of this phenomenon. At the present time the most universally accepted theory is that relating to the increase of tension on the jugular veins due to the position of the head. This bruit is heard through the entire heart cycle, over the internal jugular, sometimes loud and harsh, at the other times low pitched and soft. It is loudest at the inner third of the clavicle sometimes on one side, sometimes on the other. The murmur is almost always diminished or disappears in the prone position and is usually accentuated by moderate pressure with the stethoscope.

Eustace Smith has described a venous murmur which he claims is heard in early tuberculosis over the second interspace usually to the left of the sternum, sometimes also to the right. This sign is elicited by having the child's head extended far backward and placing the stethoscope over the left and right borders of the manubrium sterni in the second interspaces. If the head is flexed, the murmur becomes weaker, until upon reaching the normal position, it disappears entirely. Smith believed this was produced by the pressure of enlarged bronchial glands on the left innominate vein. The writer has examined many early cases of tuberculosis for this sign and was unable to find it with any constancy. On the other hand, he found this phenomenon in a few instances in association with the venous hum in normal children. He believes it to be of no diagnostic value. Although generally this murmur is without any significance, sometimes it is associated with non-pathological heart murmurs due to anemia.

Arterial murmurs are always pathological in children. They are heard best at the angle of the jaw or inner edge of the sternocleidomastoid muscles. A pressure murmur can be demonstrated often in normal children by applying a stethoscope with some force over the larger arteries. A systolic murmur also is heard very frequently over open fontanelles. This is especially common in rickets during the first year of life. Arterial murmurs over the vessels of the neck are very common in congenital heart disease.

The X-ray Examination of the Normal Heart.—The examination of the heart in the child is incomplete without the *x*-ray. There is more uniformity in the findings of skilled examiners with the *x*-ray than with any other methods by which the size and shape of the heart can be determined.

It is absolutely essential that the child be kept perfectly quiet, and the exposure should be made during diastole at the end of a deep inspiration. In the older child this can be done, but in an infant this is sometimes impossible. Some authorities believe that the lying position is the preferable one in children, but in general it seems most practical to take the exposures of children in the sitting position. This position is the most natural and the least conducive to crying. It is the easiest for the physician, the most comfortable in cases of decompensation, and also, since the measurement of the heart by percussion is usually taken in this position, it is simpler to confirm or refute the diagnosis with the *x*-ray if the picture is taken in this position.

In the sitting position the heart is subject to the smallest physiologic variations in size. In the standing position, the size of the heart is on the average about 13 per cent. smaller than in the lying, while in the sitting it is about 6 per cent. smaller than while lying. As was mentioned before, absolute quiet is most important for an accurate photograph. In the newborn, it is practically impossible to get uniform pictures. The heart is too rapid to get a sufficiently

long exposure during diastole. In infants there is a disadvantage in the fact that the anterior landmarks of the chest are vague because of the lack of ossification. For these reasons, there are as yet no normal standards for the first two years. Also during the period of infancy, the base of the heart and the vessels cannot be accurately outlined on account of the presence of the thymus.

Normally the heart of a child is obliquely oval in shape, resembling a flask, with the neck above and the body below.

In determining the size and shape of the heart, the nipples should be fixed in order to get the relations of the heart border. A line should be drawn through the middle of the vertebral column. The transverse and longitudinal diameters should be measured, the first across the widest portion of the heart, and the latter from the apex to the right upper border.

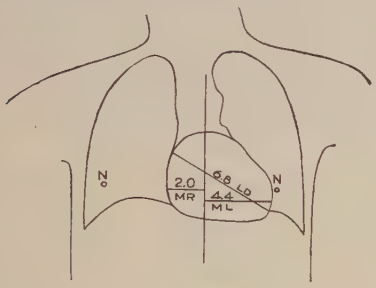

FIG. 67.—Orthodiagram of a one year old child. *N*, nipple; *MR*, distance from the right border to the midsternal line = 2.0; *ML*, distance from the left border to the midsternal line = 4.4; *LD*, long diameter = 6.8. (Taken from Reyher.)

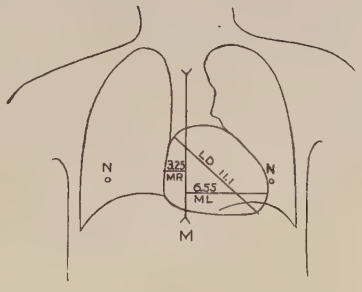

FIG. 68.—Orthodiagram of a ten year old child. *N*, nipple; *MR*, distance from the right border to the midsternal line = 3.25 cm.; *ML*, distance from the right border to the midsternal line = 6.55; *LD*, long diameter = 11.1; *M*, middle line. (Taken from Reyher.)

Although the *x*-ray gives more constant measurements than any other method of diagnosis, the results obtained by all investigators show differences in children of the same age, on account of the strong individual variations of the position and shape of the chests in different children.

Figure 67 shows the average *x*-ray picture of a child aged one year.

Figure 68 shows the heart of a normal child 10 years old.

The *x*-ray is of value in children's diseases for diagnosing physiologic hypertrophy at puberty, for recognizing congenital heart lesions, especially a dilated conus in patent ductus arteriosus, and in determining the mitral configuration. The drop heart in asthenic children, the small heart in the so-called adenoid type of child, may be diagnosed with this instrument when all other methods fail. For a detailed discussion of this subject, the reader is referred to another chapter in this System.

Polygraphic Diagnosis.—The polygraph is a precise accurate means of determining the rate, the rhythm and the relationship of the right and left sides of the heart.

It is used too seldom by pediatrists in the diagnosis of heart diseases of children. The apparatus of preference for children is the Erlanger, modified by Hirschfelder. This can be applied with suitable different side cuffs for various ages of children, and the radial, jugular and apical tracings can be taken at the same time. Successful tracings have been secured from four years up, but in the newborn and in infants, on account of the lack of coöperation and the great difficulty of getting the pulse, there are at present no standards of the normal below four years. The brachial artery is preferable to the radial in children for an arterial tracing, because it is a larger vessel.

The jugular record represents the work of the right auricle and the cardiogram shows the impact of the apex beat against the chest wall and the movements of the left ventricle.

Electrocardiography in pediatrics will occupy a complete chapter in another volume of this System.

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CHAPTER LXX

CONGENITAL HEART MALFORMATIONS

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In the early period of medicine, congenital heart malformations were of interest only to the pathologist and embryologist. Peacock was the first to make a systematic and comprehensive study of the entire subject, and his clinical treatise, published in 1855, was both accurate and complete. He divided all congenital heart malformations into two groups: malformations caused by an incomplete or arrested development of the heart; and malformations resulting from fetal endocarditis. Rokitansky, in 1875, made a classical analysis of congenital malformations with special reference to the patent interventricular septum. The signs and symptoms, which he described at that time as diagnostic of this heart lesion, have been used in diagnosis practically unchanged to this day.

Development of the Heart.—A thorough knowledge of the anatomy of the heart is a prerequisite for the understanding of the pathologic physiology and symptomatology of congenital heart lesions.

The primary cardiac tube consists of two parts, the posterior receiving the venous blood and the anterior supplying the blood to the body. As development goes on the cardiac tube becomes S-shaped and differentiates itself into three divisions: An upper, which later forms the aortic arch, a middle division making up the ventricles and a lower portion occupying the venous part of the heart.

The auricles develop to the right and left of the venous portion. Of the two openings of the auricular septum the one situated at the lower border closes at the end of the fifth week, while the opening at the upper posterior part becomes transformed into the foramen ovale. The semilunar valves become apparent at the seventh week and the auriculoventricular valves may be distinguished during the following week. By this time complete separation of the heart chambers and the two great arteries has taken place.

Congenital heart lesions are the result mainly of (1) abnormal or arrested development of the heart and (2) fetal endocarditis. Either of these factors may be the causation of one and the same lesion, as e.g., in pulmonary stenosis, and atresia, which most frequently is the result of abnormal development but which may be due to an endocarditis. A strong argument in favor of the first cause is the concomitant occurrence of several congenital defects. Rokitansky, Peacock, Vierordt, Mueller point out the presence of other congenital defects,

as mongolism, microcephalism, Darwinian tubercles, deafness and mutism, bronchial clefts, harelip, cleft-palate, polydactylism, webbed toes and fingers, coccygeal depressions, hypo- and epispadias with congenital heart lesions and vice versa. Cases are reported in the literature in which congenital cystic kidneys, spina bifida and atresia of various organs are given as the primary causes of death, and in which the autopsies revealed a simultaneous occurrence of congenital heart malformations. Vierordt found eight cases of congenital heart

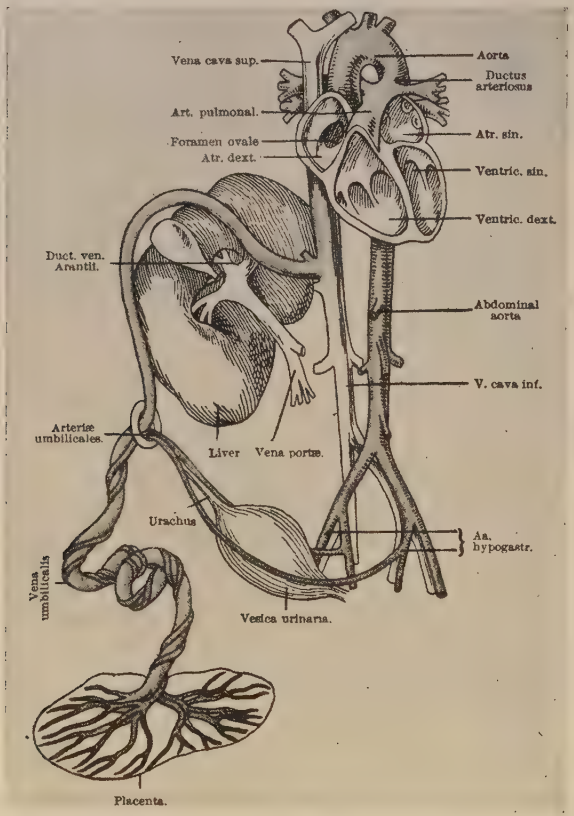

Fig. 69.—(From Pfaundler and Schlossmann, Vol. III, p. 448.)

lesions in four generations of one family. The author knows of two families in each of which one of the parents has a congenital heart lesion, and in each family two of the children have abnormal hearts.

Fright and other sudden emotions in the pregnant mother are mentioned as predisposing factors. Blood relationship is considered a possible cause. Other etiologic factors, of minor importance, however, are congenital lues, rheumatic fever, typhoid fever, small pox and other contagious diseases in the pregnant mother.

Fetal endocarditis was at one time accepted as the cause of all congenital heart malformations, but our present knowledge of embryology

leads us to think of this as a factor only in those cases with definite thickening and cicatricial contraction.

Fetal Circulation.—Figure 69 shows the fetal circulation. The pulmonary and systemic circulations are not separated in the fetus. All vessels excepting the umbilical veins carry mixed blood. The umbilical vein arises in the placenta and divides below the liver into two branches: The smaller known as the ductus venosus goes to the liver, while the larger branch empties into the inferior vena cava. The umbilical vein and the ductus venosus atrophy after birth, forming the ligamentum teres. The umbilical arteries having their origin in the hypogastric arteries of the fetus leave the body through the umbilicus and end in the placenta. Atrophy of these arteries occurs immediately after birth. The ductus Botalli, a short, thick vessel about 10–15 mm. in length, arising from the left bifurcation of the pulmonary artery, unites with the aorta at the posterior surface of the beginning of the descending arch. Unaerated blood returning from the upper extremities and the head passes through this vessel and mixes with the blood of the descending aorta. With the first respiration of extra-uterine life this vessel begins to atrophy, and as a result of lung expansion involution occurs. Usually by the tenth day of life the vessel is ligementous, the so-called ligamentum arteriosus. The foramen ovale is an oblique opening in the interauricular septum through which blood flowing from the inferior vena cava into the right auricle passes to reach the left auricle. Soon after birth the permanent extra-uterine circulation is established and the foramen ovale, no longer an essential structure, closes.

Pathological Physiology.—A fundamental knowledge of the mechanism of circulation and the pathologic physiology caused by congenital heart malformations is essential to correct differential diagnosis of congenital heart lesions. It is true that the multiplicity of the lesions (rarely do we find just one single lesion) and the continuous changes which the diseased heart undergoes render the understanding of the pathologic physiology of congenital heart malformations a relatively difficult subject. Most of the symptoms determining the clinical diagosis are directly or indirectly dependent on changes in the circulation and on the general laws of the mechanics of compensation. It is well known that the normal heart undergoes a great increase in weight and size during the first year of life, and when congenital heart lesions are present the heart is called upon not only to furnish the nutrition necessary for normal growth but also to overcome all abnormal obstacles caused by the malformation. It can be readily seen that a considerable amount of reserve power is necessary to prevent decompensation. Thus in stenotic lesions the work of the heart is greatly increased in its attempt to compensate for the smaller opening; with incompetent valves or patency of the septa the heart is required to accommodate itself to the increased amount of blood remaining after each systole. Eventually dilatation and hypertrophy result. The pathologic physiology of these lesions depends

primarily upon changes in the right side of the heart, most commonly of the pulmonary vessels and valves. Therefore pulmonary decompensation is the first and most frequent symptom, contrary to the primary cardiac manifestations in acquired heart lesions.

Another factor, equally important, has to be taken into consideration. Under normal conditions immediately after birth the pressure in the right ventricle, is greater than that in the left, the thickness of the walls and the capacity of the chambers being about equal. With the first respiration, however, the pressure in the left ventricle increases over that in the right. Between the third and sixth months the right side of the heart, especially the right auricle, becomes relatively inferior in strength and functional capacity. This physiologic change is an unfavorable factor in the prognosis in congenital heart lesions, where the right side is most frequently involved.

Patent Interventricular Septum.—In an uncomplicated patent interventricular septum the blood seeks its way through the patency flowing back and forth between the two ventricles, and if the opening is small the pressure between the right and left ventricles may remain equal giving rise to no symptoms. In the majority of cases, however, the pressure in the two chambers is unequal. Thus part of the blood is left over during the diastole, first in one side, then in the other. This in turn causes dilatation and finally hypertrophy. Usually enlargement of the right ventricle precedes that of the left, and complications may result from the accumulation of the blood in the chambers. Through the bicuspid valve blood is forced into the right auricle, then into the pulmonary circulation until finally the left auricle is affected.

Pulmonary Stenosis.—A stenosis of the pulmonary artery, at any point of its course, causes an increase of pressure in the right ventricle and a decrease in the pulmonary arteries and lungs. The caliber of the stenosis determines the amount of strain and its effect on the right heart. Unrelieved by associated lesions, the right ventricle very soon becomes dilated and hypertrophied, involvement of the auricles follows with consequent artificial tricuspid insufficiency, and venous stasis with its characteristic symptoms.

Associated lesions sometimes come to the assistance of the overburdened right heart. Very frequently the increased pressure forces the foramen ovale to remain open, thus creating a passage through which the accumulated blood flows from the right into the left auricle. Compensation is delayed, if not entirely prevented. In the presence of an open interventricular septum the blood flows from the right ventricle into the left, which in an effort to accommodate itself to the increased quantity of blood hypertrophies, and is capable of discharging the additional blood through the aorta. This affords a great means of relief. Myocardial breakdown is delayed and the prognosis of pulmonary stenosis becomes relatively favorable.

Ductus Arteriosus.—As already mentioned, a patent ductus arteriosus is nearly always associated with other lesions, most commonly with pulmonary stenosis and pulmonary atresia. When alone,

it merely relieves the aorta of some of its arterial blood supply acting as a short-cut to the pulmonary system. (Because the pressure in the aorta is greater than in the pulmonary artery cyanosis does not obtain.) Thus it partly compensates the effects of a pulmonary stenosis.

Patent Foramen Ovale.—In a pure patent foramen ovale no symptoms may be present. In more severe conditions, as in a large patency and in complicated cases, the blood because of unequal intracardiac pressure flows from one auricle into the other. This may be the means of relief to the pulmonary congestion.

Aortic Stenosis.—In aortic stenosis the blood pressure is increased in the left ventricle and decreased in the arterial system. The accumulation of the blood in the left ventricle sooner or later causes stagnation in the left auricle and pulmonary circulation. The left ventricle and left auricle become dilated and hypertrophied. The dilatation of the left ventricle results in a mitral insufficiency, which in turn leads to pulmonary congestion and dilatation of the right heart. Unless relief is afforded by some other lesion death occurs in a very short time.

Tricuspid regurgitation is a very rare congenital lesion and nearly always occurs secondarily to some other malformation. The right auricle, because of the thinness of its walls and its poor reserve power, becomes very quickly decompensated in the face of either a stenosis or regurgitation. The blood from the right auricle is forced back into the venous system, giving the most important sign of this condition, a venous pulse in the jugular vein.

Mitral Stenosis.—In mitral stenosis first the left ventricle becomes dilated and hypertrophied, later the left auricle becomes involved. The left auricle having the greatest distention capacity sometimes becomes almost balloon-like in its dilatation. Too great a distention destroys its functional capacity as is demonstrated by the disappearance of the auricular wave in the electro-cardiogram. The flow into the ventricle is usually lessened. In the presence of compensatory factors the pulmonary artery becomes dilated. This causes a pulmonary stasis and finally involvement of the right heart.

In mitral regurgitation the pressure is decreased in the aorta, and increased in the pulmonary veins and arteries. The left ventricle is the first to become enlarged, the left auricle next and the right heart completes the vicious cycle.

Signs, Symptoms, and Methods of Diagnosis.—The symptoms of congenital heart lesions, with few exceptions, are primarily the result of a distortion of the normal dynamics of the circulation of the right side of the heart. A detailed description and analysis of the most common and constant symptoms of the so-called congenital heart syndrome may be of assistance in diagnosis.

Cyanosis.—Cyanosis is the earliest, most common and constant symptom occurring in congenital heart lesions. It is present in about 90 per cent. of cases. The etiology of cyanosis is still disputed. Of the propounded theories two seem most plausible and therefore have

been most commonly accepted, though they prove correct only for the majority of cases. These theories are (1) admixture of arterial and venous blood and (2) venous stasis. Unquestionably the presence of cyanosis is correctly explained by an admixture of arterial and venous blood in some cases, in others the second theory justifies the explanation of cyanosis. On the other hand, there are congenital malformations in which cyanosis is brought about by a combination of both causes; and in others neither of the two theories is criticism proof. It has been shown repeatedly at autopsies that cases in which cyanosis has been a constant symptom did not exhibit any connection between the auricles or ventricles or any other malformations which might allow an admixture of arterial and venous blood. Again, cyanosis may occur in conditions like emphysema and bronchiectasis, where the heart is not at all involved. Also in the so-called "cor biloculate" cyanosis may be absent *intra vitam* without any ventricular septum whatsoever. One of the best arguments against the theory of the admixture of arterial and venous blood is the occurrence of the left subclavian artery arising from the pulmonary artery with perfectly normal color in the left arm. As to the theory of venous stasis one must admit that in congenital heart lesions the right side of the heart becomes quickly overburdened with subsequent venous stasis. But if cyanosis is caused by venous stasis, why then is cyanosis usually absent in acquired heart lesions where venous stasis is accepted as one of the main causes of symptoms? In the terminal stages of acquired heart lesions edema and transudates are quite common, whereas in congenital heart lesions cyanosis appears as an early symptom and edema and ascites occur but very rarely. It seems as if mechanical factors are not alone responsible for the appearance of cyanosis since in some instances this symptom remains absent for months, even years, only to become manifest when an acute infection or other form of circulatory embarrassment occurs, e.g., puberty; in such cases the diagnoses of congenital heart lesions are confirmed by autopsies.

Cyanosis varies in intensity. In the emaciated it assumes a purplish or blackish hue; in the well nourished it is rose red or pinkish. It usually occurs soon after birth to remain throughout life; it may fade with increasing age but very rarely disappears entirely. However, in some instances cyanosis does not appear until later in life. The nose, lips, finger-nails and tips, and toes are the first to be involved. Later the mucous membranes become affected, then the scleræ of the eyes and even the tongue. This symptom may be absent when the patient is at rest; it becomes more intense on crying or in any form of excitement. It may be intermittent and paroxysmal.

Cyanosis is very severe and permanent in transposition of the great vessels and in pulmonary stenosis. The diagnosis of the latter condition should not be made in the absence of cyanosis. Cyanosis may or may not be a symptom in patent ventricular septum, in patent ductus arteriosus, in patent foramen ovale and in other mixed congenital lesions.

Clubbing of the Fingers and Toes.—An almost constant symptom of congenital malformations of the heart is clubbing of the fingers and toes. It results from the same changes that cause cyanosis, and consists of an enlargement of the soft parts of the terminal phalanges with a peculiar hour-glass curving of the nails.

Dyspnea.—In congenital heart anomalies dyspnea is not uncommonly associated with cyanosis to an extent dependent upon the degree of cyanosis. In many instances the symptom is not present appearing only under the stress of excitement or upon exertion. Dyspnea occurring during nursing is frequently the first warning of a heart abnormality, and when present during the first year of life is often aggravated by coughing and crying. At times this becomes so severe that these paroxysmal attacks of dyspnea sometimes result in suffocation, unconsciousness and convulsive seizures. Such attacks usually do not last over five minutes, but not infrequently prove fatal.

Cardiac Pain.—This symptom is associated only with the most severe types of congenital heart lesions. It manifests itself in the first year of life by sudden crying out during sleep and in periods of apnea with cyanosis. Angina pectoris renders the prognosis very unfavorable and fortunately is most rarely met with in older children.

Physical Growth.—In almost all forms of congenital heart lesions with venous stasis, the physical development is retarded, if not arrested, because of insufficient blood supply to the essential organs. Nurslings, whether nursed or fed artificially, gain only little in weight. Walking is delayed. The afflicted are delicate and frail with flabby muscles, narrow faces, with thin features, and malformations of the mouth, scanty hair and abnormal growth of the genitalia are common. These patients are predisposed to attacks of acute dyspepsia and other alimentary disturbances; frequently suffer from chronic bronchitis; and in general are physically undeveloped. The greater the cyanosis the more marked is the physical inferiority. The French have described a type of infantilism which they claim to be the result of fetal endocarditis with involvement of the mitral valves. It has been the author's experience that in the milder and uncomplicated defects such as patent foramen ovale or ductus arteriosus the growth is not appreciably retarded.

Mental Development.—Children with congenital heart lesions are irritable. Their habits are unnatural. Complaints of headaches and of fainting spells are frequent, and often there is present a tinnitus aurium. In some cases the mental instability may become a definite mental deficiency, but it should not be forgotten that this condition may be due to an aplasia of the brain. It is well known that a large number of mongolian idiots have congenital heart lesions, and the author has seen congenital heart lesions in two microcephalics.

Sensitiveness to Cold.—The skin of the patient always feels cool to the touch and he usually complains of being cold in a tem-

perature in which the normal child feels quite comfortable. An increased amount of CO_2 in the blood of the extremities is thought to be the cause of the coolness of the skin. However, only in very severe conditions as in collapse following convulsive cyanotic seizures is the rectal temperature subnormal. The sensitiveness to cold bears a relationship to the degree of cyanosis.

Hemorrhages.—Petechiæ, caused by the fragility of the congested skin capillaries, are relatively common, especially in pulmonary stenosis. The eye balls are less frequently hemorrhagic, and hemorrhage into the brain is only a rare complication.

Blood.—In some types of congenital heart lesions, associated with cyanosis, and especially in pulmonary stenosis, the blood picture is markedly changed. The hemoglobin index is higher than normal, at times 160 per cent.; the red blood cells are increased in size and their number sometimes reaches 9,000,000 per c. mm.; the specific gravity is above normal, 1.071–1.081; and the alkalinity and viscosity are increased.

Retina.—When cyanosis is a constant symptom the eye grounds may reveal retinal vessels which are wide, dark, and tortuous in their course.

Murmurs.—Although murmurs are most important in the physical diagnosis of congenital heart lesions, too much stress should not be laid upon their quality and transmission in the differentiation of various lesions, because different lesions give similar types of murmurs and the murmurs themselves become quite complicated through the changes the heart undergoes. This is not to say that the murmurs in congenital malformations of the heart are not distinctive, on the contrary they can generally be differentiated from murmurs in acquired lesions. They are usually blowing or soft, although sometimes they become hissing, harsh, sawing or roaring in character. Some murmurs are heard equally loud over the entire precordium without any special punctum maximum, and indeed some are distinguishable over the entire chest and back, and in some cases as in patent ductus arteriosus they are audible even over the abdomen. Congenital heart murmurs appear chiefly over the second and third interspaces with the point of maximum intensity at the base of the heart. They are nearly always systolic in time, except in cases of patent foramen ovale in which the murmur is presystolic, and in patent ductus arteriosus in which the murmur is heard through the diastole. In cases with decompensation, with low blood pressure and very rapid respiration the murmur may completely disappear, but reappears again with improvement of the general condition.

Thrills.—Thrills are rather commonly met with in congenital heart lesions, especially in ductus arteriosus. Because of the thinness of the chest wall in infants thrills are more easily detectable at this period than in later life. The thrills in pure stenosis or in stenosis associated with other lesions are usually systolic, palpable over the base of the heart. Patent interventricular septum, alone or combined with other

malformations, rarely gives this symptom; transposition of the great vessels is characterized by its absence.

Pulmonary Sounds.—The pulmonary second sound is somewhat valuable in differential diagnosis. It is quite markedly accentuated in patent ductus arteriosus, slightly accentuated or normal in patent interventricular septum, and absent or decreased in pure pulmonary stenosis.

Percussion.—Usually the right side is the first to become enlarged in congenital heart lesions, which fact is of great aid in the differential diagnosis of congenital from acquired heart disease. The enlargement of the left ventricle is secondary and caused by other lesions. In patent ductus arteriosus a band of dullness, about 1 to 1½ sq. in., can be at times percussed over the second and third interspaces on the left side.

Precordial Bulging.—Precordial bulging depends on the amount of work required of the heart. Thus in pulmonary stenosis decompensation starts early and soon becomes marked with bulging as a prominent symptom. The area over the sternum from the second to the fifth interspace mainly to the left is the first to become enlarged.

Pulses.—In most congenital lesions a fast pulse is noticeable. In pulmonary stenosis, however, the pulse is slowed. In patent ductus arteriosus a pulsus differens has been mentioned as one of the associated signs. It was reported by Sokoloff that in some of the cases under his observation the left radial pulse was stronger than the right. The subclavian pulses may also be unequal. A pulsus paradoxicus has been observed in the condition of patent ductus arteriosus.

Roentgen Ray.—The *x*-ray picture proves itself especially valuable in the early stages of congenital heart lesions which present no objective signs. It is also of great aid in the differential diagnosis of congenital heart lesions and in older children in the differentiation between congenital and acquired lesions. In Fig. 70 (*a*) represents the large curve corresponding to the arch of the aorta. The curve of the pulmonary artery (*b*) running just below the above curve is not always detectable. Beneath this curve (*b*) the large convex line of the left ventricle (*c*) is always distinct. Figure 70, on the other hand, is the *x*-ray of a patent ductus Botalli. The band-like prominence of the upper part of the left border of the heart is equivalent to the conus arteriosus (*a*). This enlargement can only be ascribed to the pulmonary artery. With the fluoroscope it is seen to pulsate more forcibly than the aorta, whereas in the normal heart the pulmonary artery can rarely be detected. According to Grodell, the diagnosis of patent ductus arteriosus is most accurately made by the use of the Roentgen ray. In some of Grodell's cases which clinically showed an enlarged heart, and in others in which the heart appeared to be normal in size, he was able with the aid of the Roentgen ray to show the presence of a round heart, with distention and pulsation of the pulmonary artery.

The most common picture displayed on the *x*-ray plate in congenital heart lesions is the so-called mitral configuration, consisting of enlarge-

ment of both sides of the heart, especially of the right (Fig. 71). It is true that any congenital heart lesion may give this picture, but as a rule it is found most frequently in pulmonary stenosis and in patent interventricular septum associated with pulmonary stenosis. It may be well to state that in a patent interventricular septum the fluoroscope is more valuable in diagnosis than the *x*-ray plate as it exhibits a characteristic simultaneous, strong bilateral impulse of the right and left ventricles in a heart which is otherwise normal.

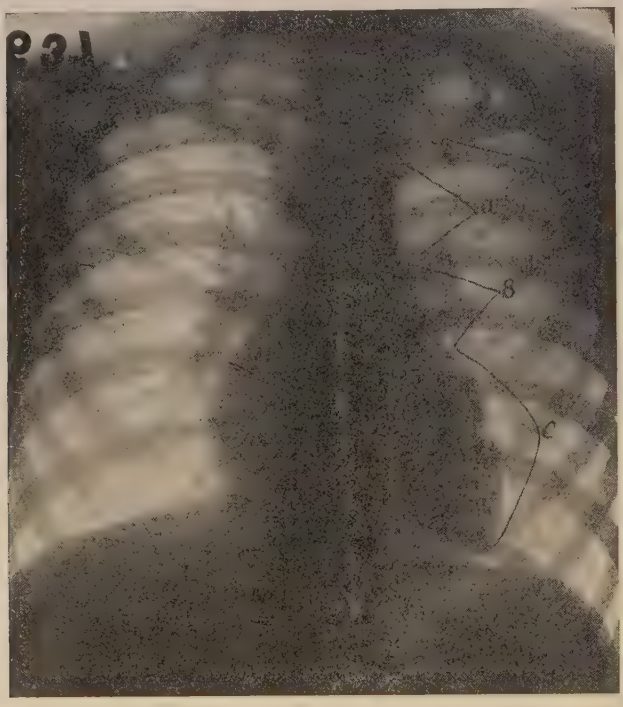

FIG. 70.—Normal heart. Boy nine years old.

The Roentgen-ray is indispensable for the confirmation of a suspected displacement of the heart, revealing the vertical drop heart before the appearance of subjective symptoms. The drop heart is sometimes an accompanying phenomenon of congenital asthenia, and in later life is associated with Glenard's disease. Credit should be given the *x*-ray for the not infrequent diagnosis of idiopathic enlarged hearts, in which there are no subjective symptoms whatsoever.

The *x*-ray plate sometimes assists in differentiating between true dextrocardia and acquired displacement of the heart to the right. In the former the entire heart is on the right of the sternum often accompanied by a complete *situs transversus*, whereas in the latter the heart may be only partially displaced to the right, with pleuritic adhesions or empyema as a part of the picture.

Chemical Pathology.—It has been thought that a determination of the chemical constituents of the blood, and a chemical analysis of body excretions might lead to diagnostic methods. Foster made a study of the creatinin, nitrogen and other chemical sustances in the body fluids in a series of miscellaneous congenital heart malformations. His results, however, are too inconstant for definite conclusions and clinical application.

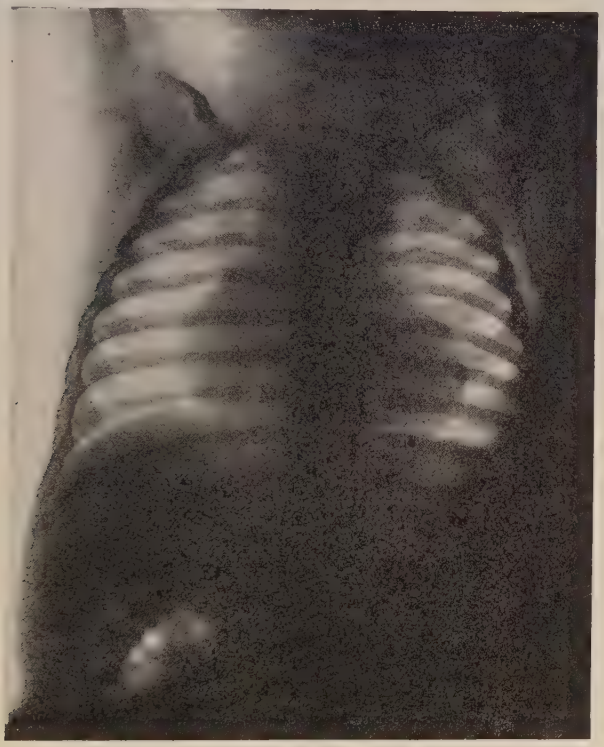

FIG. 71.—Mitral heart. Pulmonary stenosis.

Plesch Method.—This method is based on the determination of the gas tension in venous blood. Since the exchange of CO_2 between the lungs and the blood takes place in the alveolæ, the tension of the different gases in the alveolæ (according to the law of diffusion of gases) will be practically the same as in the blood.

The method consists in rebreathing a certain amount of nitrogen into an air-tight rubber bag with a tightly fitting mouth piece. The bag may be considered a large alveolæ with the same respiratory gas exchanges as the lung alveolæ. If the bag is filled with nitrogen, carbon dioxide and oxygen are given up by the blood because of the high difference in tension, until the equilibrium with the gases of the venous blood is reëstablished. Therefore an analysis of the air in the bag, that is, of the oxygen and carbon dioxide, will reveal, with the help

of the so-called dissociation curve, the quantity of gas in the blood of the lung. It is essential to observe that the expiration does not exceed the time necessary for one cycle.

Plesch determined the gas quantities in but one case, a case of persistency of ductus Botalli in which the carbon dioxide content of the venous blood was 85 per cent. as compared to 35–37 per cent. in normal. He claims that what is true for this one case must be true for other cases and he draws the conclusion that his method is of value in the differential diagnosis of septal defects, open foramen ovale, or persistency of ductus Botalli from all other lesions.

Electrocardiography.—The electrocardiograph is of some value in the diagnosis of congenital heart disease. The author investigated four cases of pulmonary stenosis, two of patent ductus arteriosus, one of foramen ovale which became closed at one year, one of transposition of the great vessels and eight of open interventricular septum. Post-mortem investigations of only two of these cases were made, and they confirmed the clinical diagnosis. The conclusions follow:

1. All congenital heart lesions do not have characteristic electrocar diograms.
2. All congenital heart lesions do not have abnormal electrocardiograms.
3. Of 16 cases clinically diagnosed as congenital heart lesions nine were diagnosed electro-cardiographically right ventriclar preponderance.
4. Of the nine so diagnosed only five were confirmed clinically.
5. The P-Q was slightly prolonged in almost all instances. However, this increase is so slight that its value for diagnosis is doubtful.
6. Two cases exhibited "exaggerated amplitudes."
7. The Q-T interval is uniformly prolonged over the normal for all ages in almost all tracings. This increase may be of value as an aid in the diagnosis of congenital heart disease.
8. The split R and S in Leads one and three are found quite frequently in the electrocardiograms of congenital heart disease.

Vital Capacity.—The vital capacity in congenital heart lesions is similar in value to that found in acquired lesions. A definite decrease has been established in decompensated cases sith cyanosis and dyspnea. It was found normal, however, in the above investigated cases of patent ductus Botalli and patent interventricular septum.

Clinically Recognized Types of Lesions.—Pulmonary Stenosis.*—From a clinical point of view stenosis of the pulmonary artery is the most important of all congenital heart lesions, forming as it does from 50–70 per cent. of this group. This condition, if uncomplicated, is fatal shortly after birth. Eighty per cent. of pulmonary stenosis are associated with a septum defect or some other congenital anomaly. The following forms are most frequently met with:

1. Stenosis and atresia of the trunk of the pulmonary artery.

* See Fig. 72. By permission of the Pathological Museum of the University of Minnesota.

2. Stenosis or atresia, or both, complicated by an open interventricular septum.

3. Stenosis and atresia in combination with one or more other lesions.

4. Pure stenosis.

The stenosis may affect either the ostium or the vessel itself; a complete obliteration, atresia, of the pulmonary artery is comparatively rare and can be only diagnosed at autopsy. Its cause is either a fetal endocarditis with definite vegetations and scar formation or the arrest in the development of the heart.

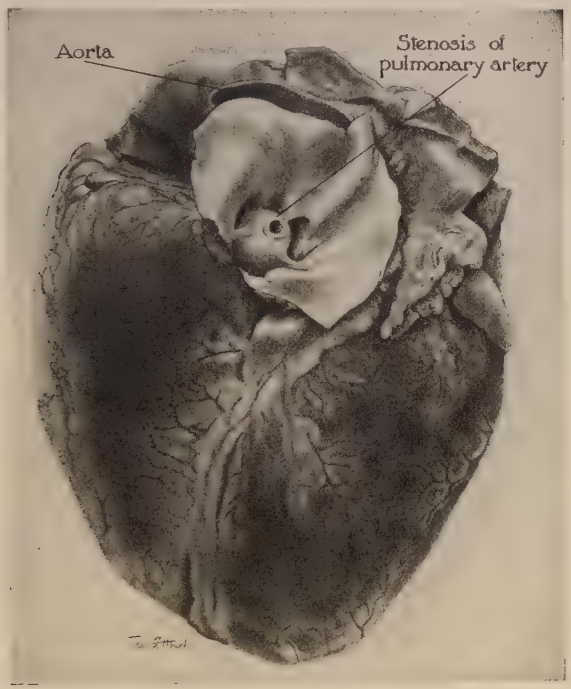

FIG. 72.

The following signs and symptoms are prominent in pulmonary stenosis, although the presence of other defects may cause some confusion in a correct diagnosis.

Cyanosis is a most constant sign, without which a diagnosis of pulmonary stenosis is unwarranted. The degree and kind of cyanosis depends on the degree of stenosis and associated lesions, and in mixed lesions it may be intermittent, appearing only upon crying or exercise. As already pointed out, dyspnea and clubbing of the fingers and toes are consequent signs.

The *precordium* becomes prominent early, usually over the third, fourth and fifth interspaces to the left of the sternum. A heaving impulse may be present. The heart becomes *enlarged* mainly to the

right and in the presence of another lesion the left side dilates also, thus displacing the apex beat downward and outward.

Probably the most important physical sign for the diagnosis of pulmonary stenosis is the *murmur*. It is always present except in complete atresia and general hypoplasia of the pulmonary artery. It is systolic in time, harsh and very loud, weakening only in the later stages. It can be heard best over the second or third interspace, to the left of the sternum. Uncomplicated it is not transmitted into the vessels of the neck, nor to the apex or axilla, being usually localized or only slightly transmitted to the left of the sternum. Complicated by a patent ductus arteriosus the murmur may assume the humming top character with transmission into the vessels of the neck. In association with septal defects it may be heard at the base of the heart persisting throughout the entire cardiac cycle. It is then transmitted toward the clavicle, and only faintly to the apex.

The decrease or absence of the *second pulmonary sound* is of great importance in the diagnosis. However, in a few instances an accentuation has been also reported by some investigators.

A *thrill*, usually systolic in time, is best felt at the base. The presence of cyanosis and thrill is considered diagnostic of pulmonary stenosis.

Bradycardia is of frequent occurrence. In decompensation the pulse becomes weakened. Unequal pulses are also found.

Polycythemia, macroerythrocytosis, an increase in *viscosity* and *alkalinity* occur. The *hemoglobin index* is increased as high as 160 per cent. The *temperature* is subnormal. In severe stenosis *angina attacks* are rather frequent. They are brought on by crying, slight infections of the nose or throat or by temporary myocardial insufficiency. During these attacks cyanosis is increased, the eyes bulge, apnea ensues. The attacks may occur during sleep. *The physical, and very often mental, development is retarded.* Such patients are usually quite irritable.

Patent Ductus Botalli.—Gibson claims the diagnosis of patent ductus Botalli to be almost as exact as a mathematical problem. He writes: "There is one particular variety of malformation so easy of detection as to be instructive even for the junior student of clinical medicine; this is the persistence of the arterial ductus."

The persistency of the ductus Botalli may not always be of clinical significance because it may be physiologically closed though anatomically open without any manifest symptoms. Uncomplicated it is relatively rare, more frequently it is associated with a pulmonary stenosis or a patent ventricular septum.

In an uncomplicated condition the symptoms do not appear immediately after birth. *Cyanosis*, absent in pure patent ductus Botalli, may become a symptom in the presence of other lesions. *Pallor* is usually present.

The most important sign for the diagnosis of this lesion is a peculiar *murmur* of great intensity more audible than in any other congenital

heart malformation. The description of its character varies with different authors. It has been described as humming top, blowing, whistling, buzzing, thundering, roaring, hissing, scraping, scratching. By some as harsh; by others as musical. Its tone color appears to the author as a rolling thunder from afar. It is equally loud at the end as at the beginning of the heart cycle. It is always heard throughout the entire systole, sometimes also through the diastole. The point of maximum intensity is usually in the second and third left interspace. It can be heard almost equally loud just below the clavicle on the left side and in the left subscapular region. It is transmitted along the left ventricle, up into the carotids, over the back, and even to the abdomen.

The pulmonary second sound is frequently accentuated.

A systolic *thrill* may be present and is best heard at the base of the heart.

Valuable in the diagnosis is a *pulsus paradoxicus.* A *pulsus differens* with the right radial stronger than the left has been reported only in a few instances. The *heart enlarges* in the later stages usually involving the right side first. Percussion may sometimes yield *Gerhardt's sign* which is a band-like area of dullness, 2 or 3 cm. wide, over the first and second interspaces, on the left side.

The presence of a systolic *pulsation* over the second left interspace was claimed only by Gerhardt. Confirmation of his assertion is still lacking.

The *x-ray plate* confirms Gerhardt's sign by a dilated conus arteriosus, which, if present, is quite diagnostic.

Interventricular Patent Septum.*—The first complete presentation of the clinical study of patent interventricular septum is that given by Rokitansky in 1875. This treatise was followed by the work of Roger, after whom the French called this condition "La maladie du Roger." Uncomplicated defects of an interventricular septum, with the exception of cases with a complete absence of the septum or very large patency, may not give any subjective symptoms. *Palpitation, dyspnea, cold extremities,* subnormal *temperature, muscular weakness, mental and physical retardation* are usually due to associated lesions.

The objective signs are quite variable. This is true especially of the murmur. The author has had occasion to study an uncomplicated patent interventricular septum in a mongolian idiot (diagnosis confirmed by autopsy) in which the murmur was at times loudest at the apex, at other times loudest at the base, sometimes it was very distinctly audible all over the heart, at other times it could hardly be heard.

This condition is rarely found alone. It is commonly associated with pulmonary stenosis and patent ductus arteriosus, which lesions make an exact diagnosis of the former difficult.

* See Fig. 73.

The *murmur* in patent interventricular septum is loud and systolic, usually obscuring the entire cardiac cycle. It is heard best at the third left interspace, transmitted to the left and right of the sternum. It is not truly transmitted to the vessels of the neck, although because of its loudness it may be heard in the neck and in the left interscapular space.

The *thrill* is also systolic, felt best at the base. The *pulmonary second sound* may be normal or slightly accentuated.

Aortic Disease.—Congenital disease of the aorta is usually inflammatory rather than developmental in origin. Four varieties of this disease are known.

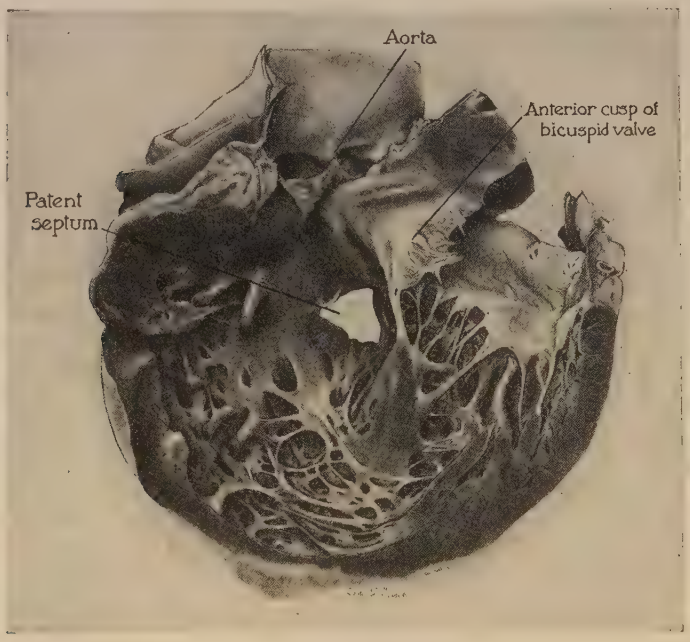

FIG. 73.

(1) Stenosis of the aorta; (2) atresia of the aorta; (3) stenosis at the isthmus; (4) stenosis at the ostium.

Stenosis of the Isthmus.—In congenital stenosis of the isthmus just below the point of entrance of the ductus Botalli, the differentiation from acquired heart lesions is impossible.

In mild cases signs resulting from the formation of a collateral circulation may be absent. The prognosis in such benign forms is relatively favorable. On account of insufficient blood supply to the arteries which are dependent upon the collateral circulation pulsation of the following arteries becomes visible: The anterior mammary, anterior intercostal; the superior intercostal, dorsal and transverse scapular; and the external thoracic. The vessels feel tortuous and solid beneath the skin. The pulse in the lower

extremities, e.g., the femoral, is very small as compared with the radial, while the aortic vessels and the vessels of the neck pulsate vehemently.

The left ventricle soon becomes *dilated* and *hypertrophied.*

A systolic *murmur* transmitted into the vessels of the neck is a constant sign. It is heard best over and to the right of the sternum at the third and second intercostal spaces.

A ringing, rebound of the pulmonary *second sound* is likely to be heard. In a true aortic stenosis this sound is decreased or absent.

True Aortic Stenosis.—In true aortic stenosis, especially in atresia, the life time is limited to a few months.

Cyanosis is always present. This symptom and an early history differentiate the congenital lesion from those acquired in adult life.

Sleeplessness, epistaxis, and plethora are common.

Headache, vertigo, buzzing in the ear.

A most definite sign is the difference in the size and quality of the *pulses* between the upper and lower extremities. The radial pulses are unequal. There may also be a marked difference in the blood pressure between the brachial and tibial arteries.

Precordial bulging and a heaving impulse appear early. The *heart enlargement* caused almost entirely by associated lesions, involves both the right and left sides.

The Roentgen-ray shows hypertrophy both of the right and left sides of the heart.

Transposition of the Greater Vessels.—Transposition of the greater vessels is rarely recognized *intra vitam.* The majority of these cases rarely survive the second month. Of 75 authentic cases only 15 lived past the second year.

The following classification of this malformation is in use:

1. *Complete Transposition.*—The aorta arises from the right ventricle and the pulmonary artery from the left.

2. *Partial Transposition.*—The aorta, instead of arising behind and to the left, arises in front and to the right, while the pulmonary artery, instead of arising in front and to the right, is found behind and to the left. Both vessels come from the same ventricle.

3. Each vessel may arise from the proper ventricle, but the relation of the vessels is abnormal through deviation of the aortic septum.

The most important symptom is *cyanosis.* However, the absence of cyanosis does not exclude the existence of this lesion, but rather indicates that the condition has been relieved by some compensatory defect. Dyspnea and other subjective signs are usually absent. The absence of a *murmur* is diagnostic. In the presence of a murmur in a congenital heart lesion the diagnosis of transposition of the great vessels becomes almost impossible.

The pulmonary second sound is usually accentuated.

The *heart sounds* are pure, a sign most valuable in differential diagnosis. The *x-ray* plate shows a dilatation to the right. A *bulging* corresponding to the enlarged pulmonary artery may also be seen.

Patent Foramen Ovale.—Patent foramen ovale is the most harmless of the congenital heart lesions. Its clinical picture is not definitely established because so few uncomplicated cases have come to a postmortem. Its occurrence, however, is relatively frequent. Hochsinger found an anatomic patency of the foramen ovale in 44 per cent. of autopsies of cases with congenital heart malformation.

Uncomplicated this condition does not give any symptoms whatsoever, only when in association with other lesions does it become of clinical importance. The most characteristic sign is a presystolic or late diastolic murmur with the punctum maximum at the middle of the sternum over the third interspace. The murmur is not transmitted.

Congenital Displacements of the Heart.—In mesocardia the fetal heart lies in the center of the thorax with its apex beat in the epigastrium.

Primary Congenital Ptosis of the Heart.—Rummo and Ferarinini ascribe this condition to a congenital ptosis of the diaphragm allowing a downward displacement of the heart. In this anatomical anomaly some of the signs and symptoms familiar to congenital heart disease are found.

Congenital Dextrocardia.—Congenital dextrocardia, *e.g.*, a complete rotation of the heart around its axis, may occur by itself, more often, however, in combination with a *situs viscerum totalis*. Percussion of the precordium in this condition gives resonance instead of the usual heart dullness—the heart area is found entirely upon the right side of the sternum. The *x-ray* confirms the percussion findings and the *electro-cardiograph* gives a record which is the exact mirror image of a normal electro-cardiogram.

Other Congenital Heart Malformations.—Atresia and regurgitation of the tricuspid valve are very rare, the latter being always secondary to the former. Both malformations are always found combined with other lesions. They are characterized by the presence of *clubbing of the fingers*, early sings of *decompensation*, by an *enlargement* to the left, by a definite *venous pulse*, and by *polycythemia*.

Mitral defects are very rare. Except for the history, a differentiation from acquired heart disease cannot be made.

Differential Diagnosis.—In many instances a differential diagnosis is almost impossible for the reason that at times two, three, or even four parts of the heart may be involved in the clinical manifestations. Theoretically speaking, the diagnosis of mixed lesions should resolve itself into an analysis and diagnoses of the individual lesions. The most important subjective and objective signs and symptoms should be made the basis for the diagnosis of a definite lesion and the remaining symptoms definitely opposed to such a diagnosis should be regarded as diagnostic of an associated lesion.

A careful, thorough examination of the patient is of the utmost importance. A complete history should be taken; murmurs should be definitely localized and studied; peculiarities of the pulses; the degree

and kind of cyanosis; the presence or absence of a venous pulse; a complete differential examination of the blood; the free use of the *x*-ray; and finally as a scientific check the electro-cardiograph, are all important in the differential diagnosis.

Differentiation of Congential Heart Lesions from Diseases with Similar Symptoms.—Cyanosis, dyspnea and clubbing of the fingers, signs nearly always associated with congenital heart lesions, may also occur in other diseases. The murmur, so valuable in the physical diagnosis of congenital malformation of the heart, may at times be absent or it may not be heard because of hurried respiration and crying.

1. Asphyxia cyanotica is usually due to breech presentation or hemorrhage from forceps delivery and appears immediately after birth. No murmur is heard in this condition.

2. Winkle's Disease. Buhl's Disease.—Marked changes in the blood of the newborn occur in these diseases, and often with associated cardiac murmurs which render the differential diagnosis from heart lesions difficult. However, the cyanosis is not a true cyanosis, the skin being a bronze color. The urine contains metahemoglobin and red blood corpuscles. The temperature is raised. In Buhl's disease also hemorrhages into the skin and viscera occur, and the cyanosis is mixed with jaundice.

3. Atelectasis.—In congenital atelectasis the cyanosis is usually intermittent, being more prominent around the face and extremities. Dyspnea is an associated sign. The heart sounds are feeble; murmurs are absent.

4. Hypertrophy of the Thymus.—Cyanosis and dyspnea occur only paroxysmally and in the last stages of the condition. No murmurs are heard.

5. Asthma.—The paroxysmal attacks in asthma are accompanied by intermittent cyanosis of varying intensity. The nature of the attacks, the wheezing and prolonged expiration and the absence of heart murmurs make the differential diagnosis from congenital heart easy.

6. Emphysema.—Cyanosis in emphysema is paroxysmal. It is more a mottling than a true cyanosis. The absence of heart murmurs, and the history of primary pulmonary involvement speak against the diagnosis of congenital heart lesions.

7. In bronchopneumonia, cyanosis and dyspnea may be present. A primary infection, physical signs in the lungs and a normal heart differentiate it from congenital heart lesions.

8. In spasmodic croup and (9) **laryngeal diphtheria** the history of an acute onset, slight fever, dysphonia or aphonia, dyspnea, most marked during inspiration, a barking cough and a normal heart aid in a correct diagnosis.

10. Retropharyngeal Abscess.—The diagnosis is based on the definite history of an acute infection with one-sided swelling of the neck, progressive dyspnea and absence of heart murmurs. Cyanosis occurs only in the later stages.

11. Cretinism.—A peculiar lividity and even cyanosis of the skin, especially of the extremities, is sometimes present. However, the characteristic facies, stature, characteristic skin and hair, and the absence of heart murmurs are diagnostic of cretinism.

12. Acidosis.—In acidosis the dyspnea is superficial, very hurried. Cyanosis may be present in the later stages. Heart murmurs are absent.

13. Acquired Heart Disease.—In older children a history of one or more attacks of tonsillitis, recurrent attacks of rheumatism, chorea and other contagious diseases is very important. However, in the early stages of acquired lesions and in mild congenital lesions without subjective signs the differentiation is very difficult. In acquired heart lesions the left side of the heart is first involved and in congenital lesions the right side The murmurs in acquired disease are apical, in congenital they are basal. The *x*-ray and the electro-cardiograph may be of assistance.

Prognosis.—Generally speaking, the prognosis of congenital heart lesions is quite serious. The earlier and the more permanent the cyanosis, the less favorable is the prognosis. Associated signs due to venous stagnation render the prognosis grave. Sometimes, after an absence of symptoms the disease may become markedly aggravated, sometimes by an intercurrent infection, at other times by an overstrain of the heart on account of excessive activity. The most benign forms of congenital heart lesions with symptoms are: Small defects of the interauricular septum, patent ductus arteriosus, and small defects of the interventricular septum. The prognosis is unfavorable in uncomplicated stenosis, ectopia, complete atresia of the pulmonary or aortic vessels, death occurring immediately after birth or within a few hours. In transposition of the greater vessels the duration of life is rarely over one year.

Sudden death may occur during paroxysms of crying. Cardiac decompensation, intercurrent infections, e.g., pneumonia, scarlet fever, erysipelas, septicemia, pertussis and measles are common causes of death. Endocarditis as a complication increases the seriousness.

Treatment.—The treatment of congenital heart lesions is unsatisfactory and almost entirely symptomatic. Two fundamental principles apply in the treatment,: conservation of the heart muscle and prevention of infections. Whenever the disease is diagnosed at birth the infant should be given the best hygiene and most careful attention. Breast feeding should be continued as long as possible. Should dyspnea make nursing impossible breast milk should be given from the bottle or by gavage. Isolation from all sources of infections, the greatest menace to this disease, must be provided. A uniform temperature is to be maintained, if necessary by application of artificial heat. A southern climate is preferable, so that the child can be kept out of doors most of the time. As in acquired heart disease a definite amount of mild exercise is indicated for older children. Exertion, however, should be avoided. The vital capacity and exercise tolerance

should be determined and the amount of work increased accordingly, since too much rest may cause a general asthenic state which is conducive to neurasthenia.

During convulsive seizures bromides are useful. Tincture of digitalis is of value only in the later stages during auricular fibrillation. Morphin is probably the most important drug in cases with marked cyanosis and dyspnea. It is best given in the form of Tinctura Opii Camphorati, one drop per month for the infant, and morphin sulphate, administered hypodermically, $\frac{1}{50}$ to $\frac{1}{75}$ gr. for a one year old child. In lesions without any subjective signs, treatment is unnecessary.

Congenital Pulmonary Stenosis.—Clinical Notes.—Patient was admitted to the University Hospital October 15, 1915, age 22 years. Fifteen years ago she had an illness which was called typhoid fever and pneumonia. Was in bed seven months at that time. Suffered from dyspnea, pains in chest, cough and expectoration, and edema of legs. The patient's appearance has always been very dark in color and she has never been well. On admission to the hospital she complained of loss of strength, dyspnea, cyanosis, headache and dizziness.

Physical examination of the heart showed a presystolic thrill and presystolic and systolic murmurs.

Hemoglobin 125; r.b.c. 8,900,000; w.b.c. 7000; p.m.n. 68, lymph. 26. Blood pressure 112–88. Urine contained a faint trace of albumin. Wassermann test was negative. Coagulation time 6–7 minutes and on November 6 a tonsillectomy was performed under local anesthesia. A profuse hemorrhage followed and patient died the same day.

Necropsy.—Well developed, fairly well nourished young woman, 163 cm. in length. Rigor is present. Lividity is marked. There is slight edema in the legs. The right pupil is 6 mm., left 5.5 mm. in diameter. There is dried blood on the lips. No jaundice. The fingers are clubbed.

Peritoneal cavity contains a few cubic centimeters of blood-tinged fluid. The peritoneal surfaces of the intestines have a dark reddish brown color. The appendix is normal in appearance and hangs free. The height of the diaphragm is at the fourth rib on the right, fifth rib on the left. Mesenteric lymph nodes are not enlarged.

Pleural cavities—right side shows no fluid and no adhesions. On the left side there are adhesions between the upper and lower lobes and over the posterior part of the lower lobe. No fluid. No exudate, hemorrhages or fibrous patches in the pericardium. The *heart* weighs 386 gm. TV 8 cm., PV = 2.5 to 3 mm. in diameter; 1.2 cm. in circumference; AV = 6 cm., MB = 9 cm. Depth LV = 7 cm. Thickness IV = 1.2 cm., RV = 2.5 cm. The heart is in the normal position. There is moderate hypertrophy and dilation of the right auricle. The foramen ovale is patent showing a large oval opening, 1.7 cm. in diameter. Below and anterior to this opening the septum is penetrated with several smaller openings. One of these is 15 mm., three others 2 mm., and three less than 1 mm. in diameter. There is an enormous hypertrophy of the right ventricle, with a marked decrease in the capacity

of the ventricle. The walls are so firm and close together that the cavity will barely admit the tip of one finger through the tricuspid valve. The papillary muscles are large. The chorda tendinæ attached to the left cusp of the tricuspid valve are short and thick. There is a slight irregular thickening along the edges of the tricuspid valve, which shows no evidence of stenosis or in sufficiency. No recent vegetation present. There is extreme stenosis of the pulmonary valve. The cusps are irregularly thickened and fused into a dome-shaped structure which shows at its apex a very small orifice, 2.5 to 3 mm. in diameter. Attached to the edge of this orifice at one side is a small soft pale-red vegetation, 2 mm. in diameter, which nearly fills up the orifice. In the conus arteriosus a short distance below the valve, several small yellowish-white tags, 4 to 5 mm. in diameter, project from the endocardium. These structures are arranged in a ring around the conus arteriosus. The endocardium above them is thickened. The pulmonary artery above the valve measures 7 cm. in circumference. The sinuses of Valsalva are deep. The wall of the artery is softer and thinner than normal. The mitral valve is normal except for small nodular thickenings near the margins of the leaflets. The aorta at the first part is 6 cm. in circumference. The coronary arteries are clear.

Diagnosis.—(1) Extreme pulmonic stenosis. Cause not determined.

2. Patent foramen ovale.
3. Concentric hypertrophy of right ventricle.
4. Hypertrophy and dilation of right auricle.
5. Acute endocarditis of pulmonary valve.
6. Congestion of lungs, spleen, liver and kidneys.

Patent Interventricular Septum.—Clinical Notes.—Case is that of a young woman, age 22 years, who was admitted to the Minneapolis City Hospital with a reserved diagnosis. The family history was negative. She gave a history of having had her thorax injured at time of birth. She had always been bluish in color. The present complaint began about two weeks before time of admittance with pain in left foot, later extending up the left knee. The pain was of a throbbing character and increased on elevation of the leg. There was an area over the posterior surface of the left femur which was hard and indurated. Fluctuation occurred later. The mass was evacuated. Diagnoses of osteomyelitis, septicemia, acute endocarditis and acute nephritis were made.

Laboratory Findings.—Blood culture was negative; urine showed albumin with hyaline and granular casts; blood gave leukocyte count of 28,000 of which 85 per cent. were polymorphonuclears.

Necropsy.—Body is that of a poorly developed, poorly nourished adult female, 152 cm. in length. There is no rigor; lividity present. Pupils measure 4 mm. in diameter. There is no edema, cyanosis or jaundice. There is a pronounced bulging of the sternocostal cartilages of the first, second, third and fourth ribs on the left side. There is an operative wound 5 cm. in length with gauze drainage located about

5–6 cm. above the knee on the external surface of the left leg. There is a moderate clubbing of the fingers.

Pericardial cavity contains about 4 c.c. of clear, straw-colored fluid.

Heart weighs 275 gm. TV = 9.5 cm.; PV = 7 c.m; MV = 11.5 cm.; AV = 5 cm. Depth LV = 8.5 cm. RV = 7 cm. Thickness LV = 1 cm.; RV = 1.25 cm. The musculature is of good color and consistence. The mural endocardium is smooth and clear and the valve leaflets show no gross lesions. There is an opening 1.5 cm. in diameter at the center of the upper portion of the ventricular septum; its margins are smooth. The thickness of the right ventricle is greater than that of the left. Root of aorta has a clear surface. The walls are very thin and the lumen small. Elasticity is good.

Diagnosis.—(1) Congenital heart defect (consisting of opening in upper portion of ventricular septum).

2. Deformity of thorax.
3. Hypoplasia of aorta.
4. Hypertrophy of right ventricle.

CHAPTER LXXI

ELECTROCARDIOGRAPHY IN CHILDREN

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Electrocardiography is that phase of cardiography which deals with the direction, the time relations and the magnitude of the "action currents" of the heart. It does not register the strength of the contraction of the heart muscle, but is rather an expression of the electrochemical processes involved in the contraction of the heart muscle.

That electrocardiography in children is a large and fertile field for clinical research, becomes evident from the many and noteworthy contributions that have been rendered with the aid of the electrocardiograph to the diseases of circulation in general; however, little or no attempt, in this country at least, has been made to investigate systematically this subject in children. The electrocardiograph offers great possibilities for studying the physiological peculiarities of the normal heart of the child; through it we obtain a clearer conception of the peculiarities of the heart mechanism during the different periods of growth; and the preciseness of the method permits us to correlate more accurately certain clinical symptoms with their associated arrhythmias and other forms of impulse disturbances. Since the electrocardiogram is an expression of the muscle rather than of the valves of the heart, we may obtain data, otherwise unobtainable, concerning the heart muscle and may hope to further our knowledge of the prognosis of heart disease.

History.—Theories of the electrical currents which gave this phase of medicine its origin were first established by Galvanio, DuBois, Reymond and others who studied the electrical changes which occur in the body under various influences of rest and action.

In 1855, Kolliker and Mueller found that with each beat of the frog's heart there could be demonstrated a definite electrical current. In 1887, Waller applied these findings to the heart of man and showed by means of a capillary electrometer that when electrodes were applied over the precordial region, definite and constant records could be obtained of the currents of the heart beat. In 1903, the famous Dutch physiologist Einthoven constructed the string galvanometer, the instrument in use at the present time.

Description of the Apparatus.—For a detailed description of the electrocardiograph and instructions for its use the reader is referred to Lewis or Kraus and Nicolai, but a few words as a general introduction to this subject may aid in a clearer understanding.

The complete apparatus consists of (1) the string galvanometer with an electro-magnet, (2) a set of electrodes, (3) an electric light for illumination, (4) an apparatus for determining the resistance of the electrodes and of the body, (5) an apparatus to determine the sensibility of the galvanometer, and (6) an apparatus for registering the photographic records of the tracings.

The string galvanometer consists of a very powerful electro-magnet, and an extremely delicate thin filament string made either of quartz coated with silver or of platinum, 2×3 mm. thick and about 75 mm. long. This string is suspended between the two poles.

There are two microscopic tubes focusing a strong light upon the string, so that the oscillations resulting from the passage of the action currents of the heart can be magnified and photographed. The size of the waves of the curves can be varied by manipulation of a screw. On tightening the string the excursions become smaller, on loosening the string a current of the same intensity will give a

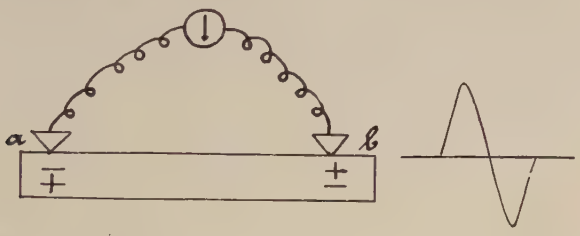

FIG. 74.—(Taken from Lewis, Clinical Electrocardiography.)

higher amplitude. A camera photographs the moving electrocardiograms.

Physiology of an Electrocardiogram.—If a strip of muscle tissue is attached to a galvanometer by two points (*a* and *b*) and one end (*a*) is stimulated by an electrode, an action current will arise (Fig. 74).

The part of the muscle at (*a*) when stimulated becomes electro-negative for the time being to the rest of the unstimulated part of the muscle. Then the electric wave passes to (*b*) causing that part to contract, which in turn becomes electro-negative to the rest of the tissue; the previously stimulated end (*a*) becomes again quiescent. The swing of the recorder is then reversed. Such an electrical phenomenon is known as a diphasic action and is the basis of all human electrocardiograms. With each beat of the heart there arise differences of electrical potential from within the heart chambers.

The tissues of the body are conductors of electricity and the extremities are in electrical continuity with the heart (the right and left arm with the base of the heart, and the left arm and the leg with the apex). The left arm is also partly associated with the left auricle. If, for example, one electrode is placed directly upon the auricles, especially near the sinus venosus, and the other upon the apex of the left ventricle, a contraction impulse is originated at the base of the great

veins, which spreads over the auricle towards the ventricle. The tissue at the electrode over the auricle becomes electro-negative, while that at the apex is rendered electro-positive. The galvanometer string then records an upward deflection which represents the auricle wave (P) in the human electrocardiogram. All upward deflections are caused in the same way, one part of the heart becoming electro-negative to another.

The Myogenic Theory of the Heart Beat.—The pediatric literature on the heart is lacking in modern nomenclature, and English and American pediatric text books, with very few exceptions, make

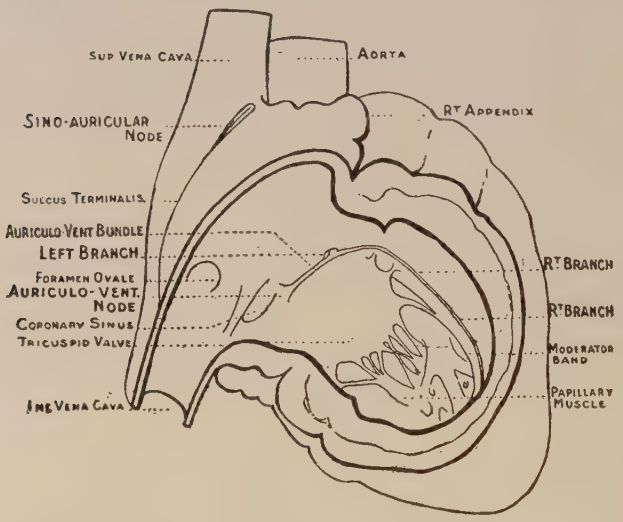

Fig. 75.—Diagram of a human heart. The walls of inferior vena cava, right auricle and right ventricle have been partially removed to expose the systa. The position of the sino-auricular node, in which the heart-beat commences, is shown, as are also the position of the auriculoventricular trunk or bundle of His. The last-named structure conveys the contraction wave from auricle to ventricle. (Thomas Lewis, Clinical Disorders of the Heart.)

no mention of the newer classification of heart disorders based upon the so-called myogenic theory.

For many years back it was believed that the heart beat depended upon the transmission of impulses generated in nerve cells to the muscle fibers of the heart. More recently, largely through the experiments of Gaskell and Engelmann, our conception of the origin of impulses and the rhythm of the heart beat has been greatly changed. At the present time the following theory is in vogue: The rythmic power of the heart resides in the muscular tissue of the heart, that is, each cardiac muscle cell has in itself the power not only of contracting in response to a transmitted stimulus, as is the case in ordinary skeletal muscle, but also of generating the stimulus within itself. There is still considerable controversy over the two theories. At

the present time the consensus seems to be that the "power of rhythmic contraction is inherent in cardiac muscle fibers."

Figure 75 shows schematically the anatomy and physiology of the conducting system by which impulses are transmitted through the various chambers of the heart resulting in the contraction of the heart muscle.

The beat of the heart consists of contractions of the chambers *in proper sequence*, the contraction of the ventricle following that of the auricle. The impulse stimulating the contraction of the heart muscle begins in a mass of tissue known as the sino-auricular node which lies imbedded in the upper and anterior end of the sulcus terminalis

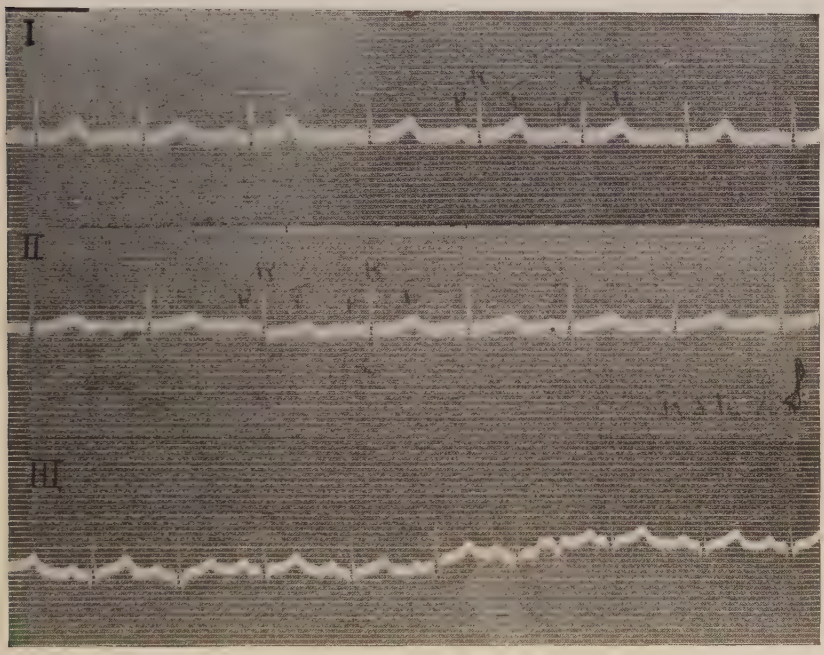

FIG. 76.—Normal electrocardiogram of boy of 11 years. P-R = 12 seconds. Rate 108.

or the beginning of the right auricle. This impulse then spreads through a special band of tissue, the auriculoventricular bundle, through the septum of the ventricles to the right and left chambers.

The Normal Adult Electrocardiogram.—Figure 76 is an electrocardiogram of a normal boy, 11 years old. At that age the characteristics of the adult obtain. As explained before, Lead I (first tracing) represents the auricles and the top of the ventricles. The second tracing, Lead II, represents the oblique diameter from the aortic arch down through the apex of the left ventricle, and the third tracing, Lead III, is the result of the action current passing mainly through the left side of the heart. With these three leads the entire heart is encompassed.

The middle curve represents the most constant average of the electrical potential of a given heart. The heavier horizontal line is the base line which shows the position of the string when no current passes, and the letters P, Q, R, S and T represent different phases of the heart beat. The upward deflections P, R and T are very important and best understood, while the significance of Q and S downward waves is still in dispute.

P represents auricular activity. It is usually two scale divisions high (one scale division represents one-tenth millivolt of current). The other deflections represent ventricular activity. R, the most important of all waves, is thought to represent the emptying of the ventricles, its summit marking the instant when the contraction has reached the apex of the heart. It is usually ten to twelve scale divisions high in Lead II and about five to six divisions in the other two Leads. T is the final wave of the ventricular complex. It is usually directed upward; at times it may be inverted in normal conditions, especially in Lead III. It is about 2 mm. high in Lead I, about 2.5 mm. in Lead II and as high as 5 mm. in Lead III.

A downward wave, represents the initial contraction of the fibers of the apex, according to Einthoven. It is always small and even absent in the electrocardiogram of a normal heart. Very little is known regarding the significance of the S wave in the normal electrocardiogram. It follows the R wave and reaches below the base line; it averages about two scale divisions in Leads I and II and one and a half in Lead III.

If a standard apparatus is used and accurate technique employed, the tracings obtained from normal hearts are quite constant and precise.

ELECTROCARDIOGRAM IN THE NORMAL CHILD

The first investigation of the electrocardiogram of the child was undertaken in 1908 by Funaro under the direction of Nicolai. He studied the electrocardiograms of 45 children, mostly infants, and discovered the deep S in Lead I in nurslings. This observation has since been corroborated by other investigators. Funaro's work is open to criticism, however, in that he employed only the first lead, nor did he state whether his subjects had normal or abnormal hearts.

A little later, though in the same year, Heubner made a similar study, making tracings of the first derivation only. He took the electrocardiogram with the subject asleep or administered chloral-hydrate to keep him quiet. Among his observations on newborns were the deep S and the very small or absent R. Heubner thought that the change from the infantile type of electrocardiogram to that of the adult took place at about the eleventh or twelfth month. Hecht, in 1912, contributed the first comprehensive and complete treatise on the physiological peculiarities of the heart of the child. However, he neglected to establish a composite curve as a guide for the normal at all ages of childhood.

Krumbhaar and Jenks, in 1916, derived their composite electrocardiograms from a study of 45 normal children of all ages. Since then no attempt has been made to investigate the peculiarities of each of the deflections of the normal electrocardiogram at different periods of childhood.

Technique Procedure.—It is much more difficult to employ the electrocardiograph in children than in adults, and for this reason it is especially important to mention some of the difficulties met with in working with children.

The right arm, left arm and left leg of the subject are connected to the electrocardiograph by means of copper electrodes. In working with newborns I used small, tightly fitting copper cuffs held together by rubber bands. For older children the electrodes used for the adult are suitable. The skin area which comes in contact with the electrodes must be cleansed with soap and water, because the presence of fatty substances on the skin surface increase the resistance to the electric current. The skin current, of the same magnitude as in adults, is compensated by throwing into the circuit an equivalent amount of current in the opposite direction.

The position of the electrodes must be watched carefully, especially in nurslings. The slightest movements will loosen the electrodes and cause low deflections. The bare legs or arms must be kept from touching each other to avoid crossing of the current.

Absolute quiet is the most important factor in securing accurate tracings. In working with infants, it is very difficult to keep the string in the proper position. The slightest movement throws the string out of the field. It is especially important that the string be neither too tight nor too loose. Coughing, sneezing, or crying will cause marked deflections of the string. Tracings obtained under such conditions must be discarded. In the newborn electrocardiographic tracings are taken preferably while the subject is asleep. A nipple placed in the infant's mouth for a few minutes before starting the experiment will often keep him quiet long enough to take a satisfactory record. In young nurslings the attention can be held by a lighted match or a bright object.

All records were obtained either at the Heart Station at Millard Hall of the University of Minnesota or at the University Hospital, 400 feet away from the electrocardiograph. At first, at least two tracings were taken at each sitting, in some instances three or more. It was found that although the height of the deflections differed slightly in the same subject the form was quite constant. It was not necessary to administer drugs in order to obtain satisfactory records. Three leads were taken for each child. The children selected were within normal limits of weight and height, with chests of normal shape, and hearts that showed no abnormal signs. The same technique was applied for all children. The child lay on his back in a perfectly quiet room, and the time selected was usually between 9 and 11 in the morning after the first feeding. The same electrodes were always

used. Pads for the electrodes were washed in soap and water, boiled and finally immersed in saline solution. The string was so adjusted that one millivolt of current caused a deflection of 1 cm. Platinum strings of about 3500 ohms resistance and of .02 second deflection time were employed. It was found that body resistance does not vary appreciably between newborns and older children. All the tables inserted are calculated on the basis of one millivolt = 1 cm.

P=wave.—It is the consensus among all authorities that the P-wave represents auricular activity. Although there are exceptions to the rule the height of P may be considered as representative of the summation of action currents in the auricles, while the distance from the beginning of P to the beginning of R (the so-called P-R interval) represents the period of impulse conduction through the auricles and through the conducting tissues to the ventricles.

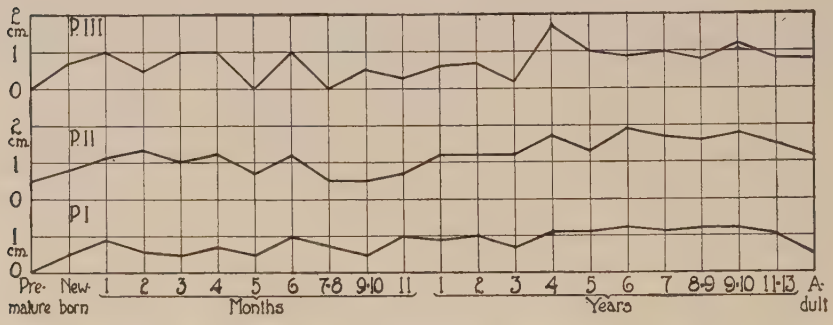

FIG. 77.—Height of P deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

Hecht has attempted to establish a normal P for childhood, by dividing the height of R by the height of P of the same lead, thereby deriving at what he terms the "Auricular Quotient." He found that in newborns the Quotient was 68 per cent. and in older children (taking the average of all children from 2 to 13 years) 12.5 per cent. I do not believe this method a reliable guide for the height of the P. In the first place Hecht took only derivation I, whereas throughout childhood P in Leads II and III is higher than in Lead I; secondly, in order to have an accurate guide for all ages, it would be necessary to divide childhood into at least four periods instead of two; thirdly, in very young infants, especially in newborns the R in Lead I is small, thus decreasing the quotient for the entire four periods of childhood. Linetzky, working with adults only, found that P did not vary with age. His averages for the height of P were from 1.2 to 1.3 mm. for the ages of 20 to 50.

In my own investigations I found the following (Fig. 77):

In two premature babies none of the three leads shows the auricular deflection. From birth through the entire period of childhood P is constant and definite. In only two electrocardiograms of the entire

series is P absent. In general P in childhood is higher than in the adult. The average of P in derivation I is .6 mm.* for the first 2 years; from 2 to 13 years it is 1.0 mm., as compared with .5 mm. in the adult. During the first few months of life P is higher than in the adult although not quite so broad. In Lead II, the average of *P* is 1.2 mm. for the period of infancy and 1.5 mm. for the latter part of childhood. It can be seen that P_2 is higher throughout childhood than in later later life. Beginning with a height of .5 of a scale division at birth, it abruptly increases during the first few months to slightly over one scale division. During the remainder of childhood it runs as high as 2 mm. as compared to an average of 1.2 mm. in the adult. The height of this deflection in Lead II is less constant than in Leads I and III.

In a series of 111 cases eight records exhibited either a diphasic or an inverted P-wave; six of these were in newborns, one in a child three and one-half years old, the other in a child of six years. In two cases P_1 and P_3 were inverted.

The clinical significance of an electro-negative P has not yet been definitely established. Carter, in an investigation of the inverted P in derivation III, concluded that it was caused by (1) an ectopic rhythm as the result of a definite change in the location of the pace maker, and by (2) disturbances in the respiratory rhythm. Hè found that P, especially in Lead III, was very much influenced by the different phases of respiration; that P was lower at the end of respiration than at the beginning; and that the slight rotation of the heart about the sagittal axis of the body, brought about by a very deep inspiration, also changed the height and shape of P.

Goddard noted the great frequency of an inverted P_3. In 700 cases P_1 was inverted in 4, P_2 in 7 and P_3 in 75 instances.

If we are allowed to assume a direct relation between the size of P and the structure of the auricle, the relatively high P during the first year of life may be readily explained by anatomical data. We know that in a large number of instances the foramen ovale remains open until the end of the first year, thus increasing the work of the auricles. Furthermore, Gundobin states that during the first year the auricles are 21 to 22 per cent. of the weight of the ventricles as compared to 20, 18 and 17 per cent. in the following years.

There is no greater frequency of abnormal P-waves in my series than in those reported on normal adult hearts.

Q=wave.—There has been and still is a difference of opinion as to the physiological significance of the Q deflection. Q is a downward deflection at the beginning of the ventricular complex. Hoffman believes that the Q deflection represents the beginning of the ventricular impulse conduction. This explanation seems to be most commonly accepted. According to Lewis, Q in Lead I represents the spread of left ventricular activity and in Leads II and III he believes it to be a right ventricular event.

*1mm. = 0.1 millivolt = one scale division.

Krumbhaar noted the relatively deep Q in childhood, especially in Leads II and III. In these leads the average of Q in the adult is less than 1 mm.; whereas for the infants the Q is relatively and absolutely deeper.

In my series I find that in general the Q of Lead II and III is deeper than in the adult (Fig. 78). Up to the first month, Q is

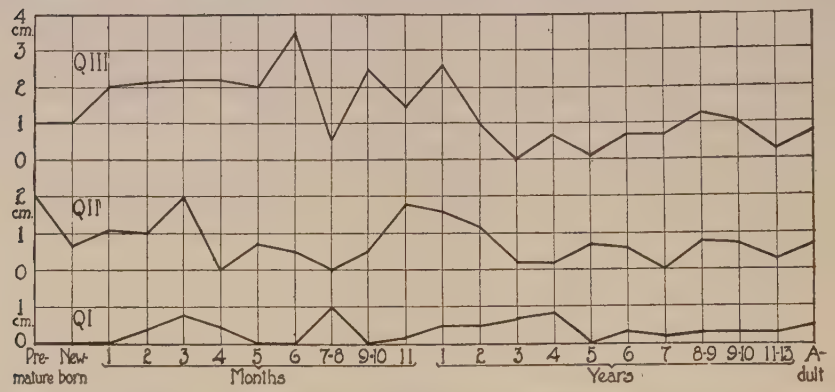

FIG. 78.—Height of Q deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

absent in Lead I; from the first to the fifth month, Q_1 is variable and indefinite, never reaching deeper than .7 mm. From the eleventh month on, there is a gradual increase of Q_1. From the fifth year on there is a remarkable constancy of the Q persisting throughout the remainder of childhood, averaging about .4 of a scale division (approximately the same as in the adult). The absence or at least low depths of Q_1 during the first year and its increase later on corroborates the theory of Lewis that Q_1 represents left ventricular activity. Q_2 is not quite so uniform in its depth. During the first three months it is rather deep running on an average of one scale division. From the fourth to the ninth month, it remains more uniformly at the level of one-half of a scale division, and from the ninth month to the second year it increases to 2 mm. From the third year on, it averages .5 mm. which is slightly less than in the adult. During the first period of life Q_3 is deeper than Q_1 or Q_2. From the fifth month to the second year it is somewhat variable. At two years there is a sudden diminution and the figure remains low throughout the rest of childhood. The average for the first two years is .9 of a scale division. From two years on Q_3 is .6 mm.

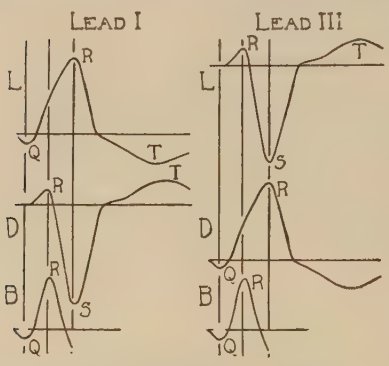

FIG. 79.—Schematic diagram of levogram, dextrogram and bigram. (Taken from Lewis, "Clinical Electrocardiography.")

If Lewis' theory that Q_1 represents left ventricular activity and Q_3 right ventricular activity is correct, then the depths of this deflection in the third derivation (Fig. 79) gives corroborating evidence of a right ventricular preponderance in nurslings.

R=wave.—The R-wave is the most important and most constant of the electro-positive deflections of the ventricular complex. There is, however, some difference of opinion as to the physiological significance of this wave. Hoffman believes the R-wave to represent the impulse conduction through the ventricular fibers or the excitation of the muscle immediately preceding the actual contraction.

Linetzky found that in adults the R-wave became higher with age and with an increase of the heart size. The average height in his series of 300 adults was from 11 to 14 mm. (Lead II). In my study R generally becomes much higher (Fig. 80) than is true for the adult; in Lead I, however, R is lower in the premature and in the newborn than at any other period of life. After the first month there is an abrupt ascent with the peak falling in the fourth month. From then on, until the fourth year, the averages form an up and down curve. For the second and third year, I used the average of only two cases. This may account for the unexpected drop of the R-wave after there had been already an ascent. The high R after the fourth year is suggestive of a change toward preponderance of the left ventricle.

R in Lead II shows a very definite ascent; this is consistent with the anatomical change in the mass relationship between the right and left ventricle. No R_2 was found in the premature, but immediately after birth R_2 rises very rapidly. From the first year to the fourth the curve runs about the same. From the fourth year on, there is another increase surpassing the adult height at six years; it then becomes higher and higher so that at puberty it averages 15 mm. as compared to 10.3 mm. in the adult.

R_3 is variable throughout the entire period of childhood. It is absent in the premature but during the first month of life it reaches a rather high measurement which it retains until the fourth month. For some unknown reason it falls and stays at a low level until the eighth month. From then on, until the fourth year, it is again variable. After that it increases and remains high throughout the rest of childhood. For the first two years it averages 5.5 mm., from then until 13 years 5 mm.

S=wave.—The S deflection is still a subject of dispute. It is not always found in the normal electrocardiogram.

In Lead I, S is a right ventricular event and in Lead III it is a left ventricular event. As far back as 1908 Funaro working with Nicolai found a deep S in a large majority of the 45 infants examined. Nicolai concluded that this was due either to a left ventricular hypertrophy or to a more horizontal position of the heart at that age.

At almost the same time Heubner noticed this characteristic deep S_1. The presence of a deep S in earliest childhood has become

an established fact. There is, however, some difference of opinion as to when the deep S disappears. Some believe it disappears as early as

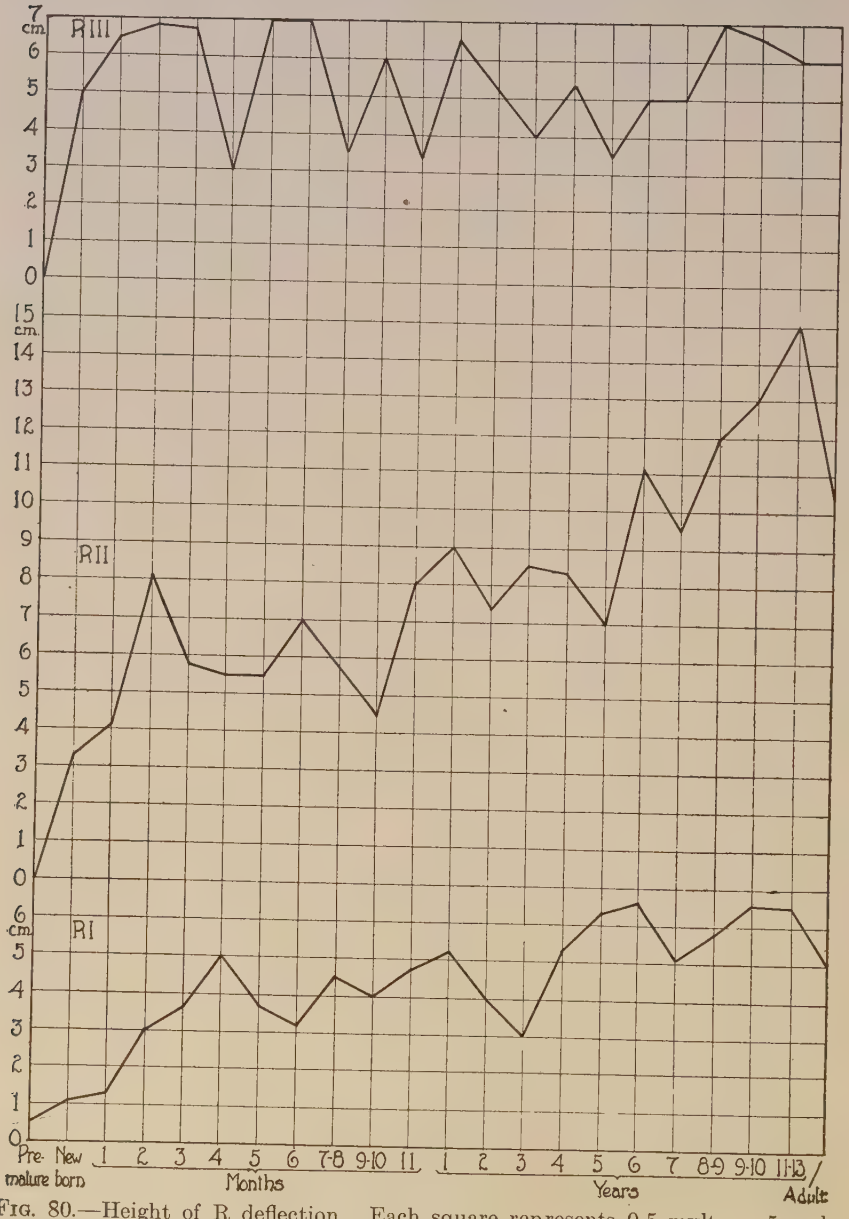

FIG. 80.—Height of R deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

the third month; others at about the seventh or eighth month; while other observers are not sure of a permanent change until the end of the first year. There is also a difference of opinion among the

earlier investigators as to the interpretation of this characteristic wave. Is it due to a higher and more horizontal position of the heart on account of the high diaphragm in childhood, or is it due to the fact that in that period the right ventricle is relatively preponderant over the left? My experiments confirm the opinion of Grau and others that change of position is without any influence on the shape of the S-wave. On the other hand, using the formula of White $(U_1 + D_3) - (D + U_3) =$ constant for the determination of the ventricular preponderance and comparing the electrocardiograms of the period of infancy month by month with the size and thickness of the ventri-

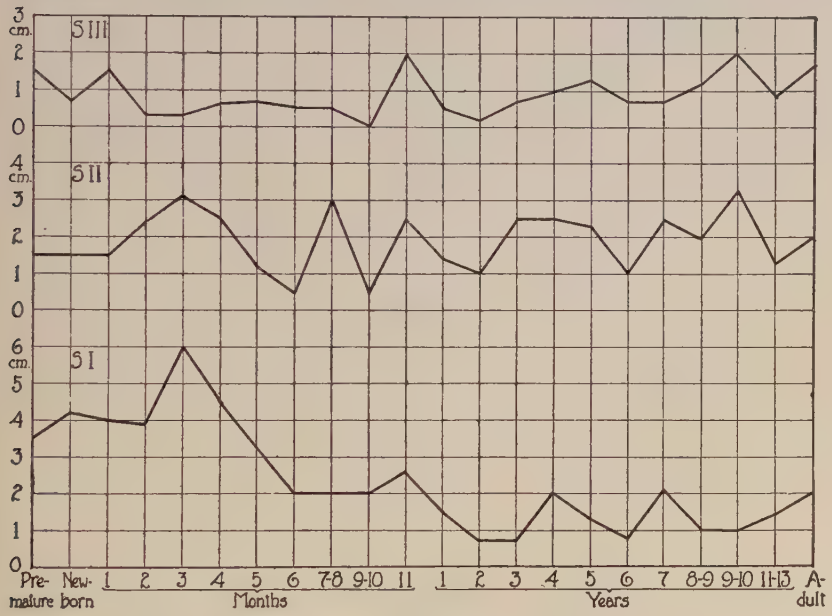

FIG. 81.—Height of S deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

cles of the same ages, one is justified in concluding that the explanation of the deep S in Lead I lies in the anatomical relationship between the right and left ventricles.

In my series, S_1 is both relatively and absolutely greatest during the first three months of life (Fig. 81). From its peak at the end of the third month it diminishes abruptly to the sixth month. It remains on a level until the tenth month, to diminish again until it finally reaches its minimum deflection at about the beginning of the second year. From then on it increases slightly and remains about the same throughout the rest of childhood. In the latter part of childhood it is slightly deeper than in the adult.

S in Lead II is generally lower during the period of infancy than in later childhood. After the third year it is about one scale division higher than during the period of infancy.

S in Lead III shows a curve somewhat similar in its inconstancy to S in Lead II. The average of S_3 for the entire period of childhood is lower than that of S_2. From birth to the third year the curve is too variable to allow any conclusions; from the third year on, the wave becomes more constant, averaging however less than in the adult.

The influence of crying, respiration and position upon the shape and size of the S-wave have all been studied. The occurrence of a deep S_1 in older children will be discussed in another paper in connection with atypical electrocardiograms in normal children.

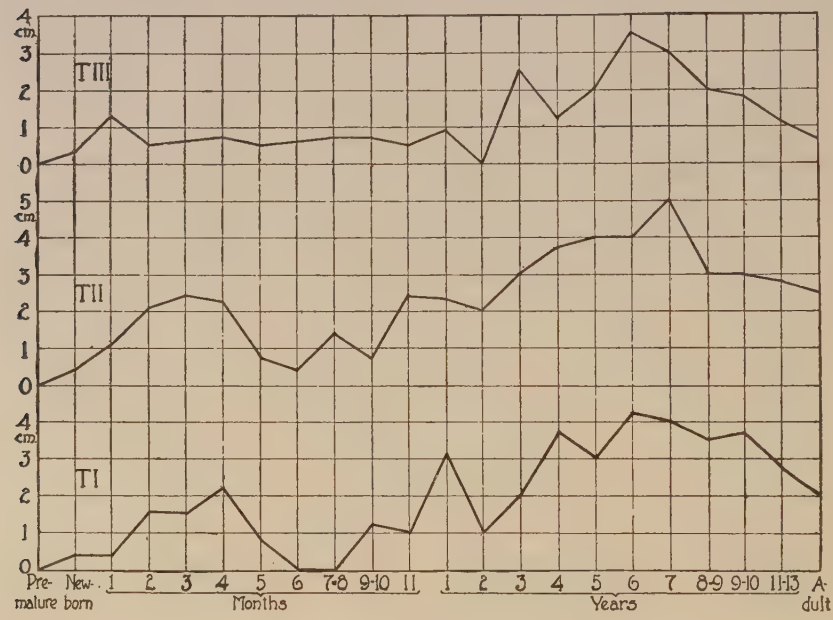

FIG. 82.—Height of T deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

T-wave.—The T-wave is the last of the ventricular complex. There is still a difference of opinion as to its meaning, but the most tenable theory seems to be that it accompanies the contraction of the ventricle. According to Linetzky the T-wave in the adult decreases with the increase of age, and is smallest in the very old. At about 45 years of age it is quite constant (3 mm.). From then on, it decreases to 2.1 mm. The decrease of the T-wave is in direct proportion to the increase of the R-wave. Krumbhaar in his work with children found T absent in the first week of life, but constantly present after the third week, being highest in Lead II, and lowest and frequently inverted in Lead III. Hecht found it present in the newborn, although not uniformly.

In the child T is the phase of the ventricular complex most susceptible to unexplained changes. In my series of 22 cases I found no T in the premature, but just after normal birth during the first 10 days

it was present in 39 per cent. of cases in Lead I, in 77 per cent. in Lead II and in 47 per cent. in Lead III (Fig. 82). After the first month it was quite constant. T in Lead I was more regular in its developmental changes than in the other two leads.

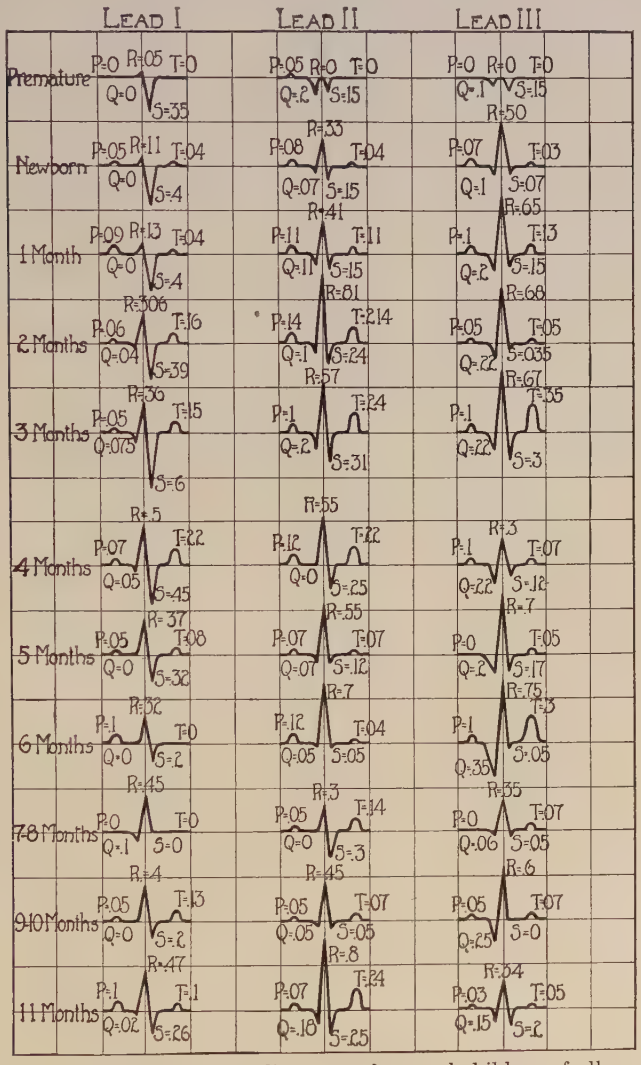

FIG. 83.—Composite electrocardiograms of normal children of all ages. Exact heights of all deflections in millivolts. Each square represents 5 scale divisions of 0.5 mvlt. (See Fig. 84 on p. 296 for a continuation of this figure.)

In Lead I, from the first to the fourth month, there is a sudden increase to be followed by a sudden drop until the seventh month. It then increases until the second year. I can see no physiological explanation for such a change. From the second year on there is

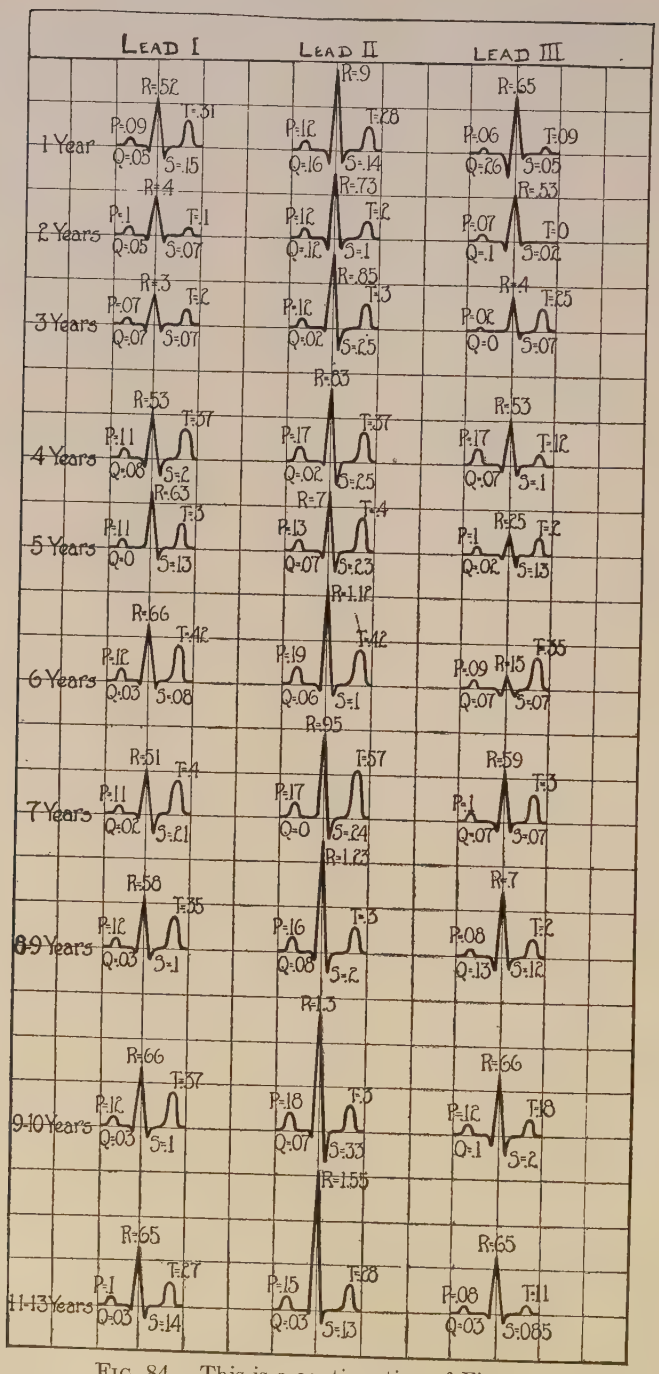

FIG. 84.—This is a continuation of Fig. 83.

TABLE 1.—Twenty-Two Normal Electrocardiograms of Infants Aged from 1 Hour to 11 Days

No.	Age	Weight, Gm.	Sex	P			Q			R			S			T			Rate
				1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
1	Premature 7 mo. 3 da.	2,110	M	0	0.1	0	0	0.3	0.2	0.1	0	0	0.4	0.2	0.1	0	0	0	176
2	Premature 8 mo. 1 wk.	2,310,	M	0	0	0	0	0.1	0	0	0	0	0.3	0.1	0.2	0	0	0	180
3	4 hours	3,115	M	0	0	0	?	0.02	0	0.3	0.32	0.15	0.3	0	0	?	0	0	110
4	8 hours	3,440	M	0.09	0.1	0.1	0	0.15	0.25	0.15	0.5	0.8	0.5	0.15	0.09	0	0	0	108
5	16 hours	2,840	M	0.1	0.15	0.05	0	0	0.1	0	0.3	0.45	0.25	0.2	0.2	0.18	0.02	0	152
6	18 hours	2,440	M	0.10	0.05	0	0	0.1	0.05	0.05	0.5	0.3	0.3	0.1	0	0	0	0	160
7	24 hours	3,600	M	0.05	0.15	0.05	0	0.01	0	0	0.22	0.35	0.22	0.15	0	0	0	0	102
8	2 days	3,230	F	0.1	0	0	0	0.05	0	0.2	0.3	0.75	0.3	0.2	0	0	0	0.05	135
9	2 days	3,125	M	0	0	0	0	0.1	0.1	0.1	0.25	0.3	0.3	0.15	0.05	0	0	0.09	
10	2 days	2,940	F	0.05	0	0.05	0	0	0	?	0.05	0.09	0.3	0	0.09	0	0	0	128
11	2 days	3,625	F	0	0.1	0.08	0	0	0	0.1	0.1	0.09	0.4	0.09	0.1	0	0.1	0	128
12	3 days	3,095	M	0.05	0.1	0.1	0	0.1	0.1	0.1	0.4	0.4	0.6	0.15	0	0.05	0.05	0.1*	
13	3 days	3,250	F	0.1	?	0.1	*	?	0.2	0.3	*	0.9	0.7	?	0.2	0.2	?	?	
14	4 days	3,810	M	0.1	?	0.1	0	?	0	0.2	*	1.0	0.7	*	0	0	0	0	132
15	4 days	3,100	M	0.1	0.15	0.1	0	0.1	0.1	0.1	0.4	0.5	0.5	0.2	0.05	0.1	0.1	0.09	130
16	4 days	2,800	M	0.15	0.1	0	0	0.1	0	0.5	0.3	0.2	0.4	0.3	0.2	0.05	0	0	140
17	5 days	2,790	F	0	0.05	0	0	0.05	0.05	0.05	0.1	0.1	0.3	0.1	0	0	0	0	174
18	5 days	3,420	M	0.1	?	0.1	0	?	0.2	0.3	?	0.9	0.7	?	0.2	0.2	?	0	135
19	5 days	2,720	M	0.05	0.1	0.08	0	0.05	0.15	0.1	0.2	0.3	0.5	0.05	0.05	0.05	0.09	0.08	202
20	6 days	3,440	F	0	?	?	0	?	?	0	?	?	0.2	?	?	0	?	?	172
21	9 days	4,000	F	0	0.15	0.05	0	0.1	0.1	0.1	0.5	0.4	0.3	0.3	0.2	0	0.1	0.09	160
22	9 days	4,000	F	0	0.2	0.25	0	0.15	0.3	0	0.5	0.7	0.5	0.3	0	0	0.1	0.5	180

One scale division represents 1 mm. in actual height and 0.1 mvlt. in potential.
* indicates inverted.

TABLE 2.—Forty-Five Normal Electrocardiograms of Infants Aged from 11 Days to 1 Year

No.	Age	Weight, Gm.	Sex	P			Q			R			S			T			Rate
				1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
1	11 days	2,815	F	0	0.05	0.1	0	0.05	0.1	0.05	0.04	0.5	0.4	0	0.05	0	0.1	0.2	148
2	13 days	3,200	F	0.1	0.09	0.1	0	0.1	0.2	0.1	0.5	0.6	0.5	0.2	0.3	0	0.1	0.1	136
3	18 days	2,440	M	0.1	0.05	0	0	0.1	0.05	0.05	0.5	0.3	0.3	0.1	0	0	0	0	160
4	24 days	3,360	M	0.1	0	0	0	0	0	0.15	0.15	0.2	0.6	0.15	0	0	0.05	0.09	132
5	3 wks.	3,800	M	0.1	0.15	0.1	0	0.1	0.2	0.3	0.8	0.6	0.4	0.3	0.1	0.1	0.2	0.1	124
6	3 wks.	3,600	M	0.1	0.1	0.1	0	0.2	0.3	0.1	0.4	0.9	0.3	0.1	0.2	0.05	0.1	0.1*	128
7	5 wks.	4,115	F	0.05	0.1	0	0.15	0.3	0.1	0.3	0.9	1.2	0.7	0.5	0.6	1.5	0.4	0.3	136
8	5 wks.	4,030	M	0.15	0.2	0.1	0	0	0	0.1	0.6	0.8	0.4	0.3	0.1	0.1	0.1	0.1	128
9	6 wks.	3,840	F	0.1	0.15	0.1	0	0.3	0.4	0.5	1.0	0.9	0.6	0.4	0.1	0.2	0.2	0.2*	110
10	6 wks.	3,900	F	0	0.1	0.05	0	0.25	0.3	0.3	1.0	1.0	0.4	0.3	0.15	0.05	0.05	0	147
11	6 wks.	3,143	F	0.1	0.15	0.05	0	0.1	0.15	0.15	0.6	0.8	0.6	0.1	0	0.15	0.2	0.1	165
12	6 wks.	3,820	F	0.1	0.15	0.09	0	0.05	0.1	0.35	0.4	0.4	0.4	0.25	0	0.15	0.1	0.1	140
13	6 wks.	3,720	F	0.05	0.1	?	0.05	0	?	0.3	0.3	?	0.1	0.1	?	0.05	0.05	?	
14	6 wks.	3,915	F	0.05	0.05	?	0	0.15	?	0.15	0.6	?	0.35	0.45	?	0.1	0.15	?	
15	2 mos.	4,300	M	0.1	0.1	0	0.05	0.1	0.2	0.3	0.8	0.6	0.3	0.1	0.1	0.1	0.4	0	160
16	2 mos.	4,500	M	0.1	0.09	0	0.1	0.2	0.4	0.2	0.1	1.0	0.4	0.2	0	0	0	0	
17	2 mos.	4,560	M	0.1	0.1	0.1	0	0	0.2	0.5	0.55	0.4	0.8	0.25	0.3	0.1	0.2	0	180
18	7 wks.	4,320	M	0.05	0.2	0.05	0	0.05	0.15	0.5	0.3	0.3	0.4	0.25	0.05	0.2	0.4	0.1	150
19	7 wks.	4,020	M	0.05	0	0	0	0.1	0.1	0.2	0.25	0.1	0.35	0.2	0.05	0.1	0.1	0.1	
20	10 wks.	4,940	F	0	0	0.1	0.1	0.3	0.4	0.4	0.6	0.3	0.5	0.8	0.3	1.5	0.2	0.2	148
21	12 wks.	6,110	M	0.1	0.2	0.1	0.2	0.3	0.3	0.3	0.6	0.7	0.5	0.3	0.8	0.3	0.4	0.6	136
22	3 mos.	5,840	F	0	0.2	0.2	0	0.2	0.2	0.6	0	1.5	0.8	0	0.1	0	0.3	0.5	120
23	3½ mos.	6,120	M	0.1	0.05	0.09	0	0	0.15	0.3	0.3	0.2	0.4	0.2	0.15	0.15	0.05	0.05	117
24	4 mos.	6,580	M	0.1	0.2	0.15	0	0	0.3	0.6	0.8	0.4	0.5	0.3	0.1	0.3	0.4	0.1	150
25	4 mos.	6,850	M	0.05	0.05	0.05	0.1	0	0.15	0.4	0.3	0.2	0.4	0.2	0.15	0.15	0.05	0.05	130
26	5 mos.	7,100 Lbs.	M	0.09	0.1	0.1	0	0.05	0.05	0.4	0.4	0.2	0.4	0.1	0.5	0.15	0.1	0.1	150
27	5 mos.	15	M	0.05	0.05	0	0	0.1	0.09	0.5	0.5	0.2	0.4	0	0	0.1	0	0.12	185
28	5½ mos.	14	M	0.1	0.05	0	0	0.1	0.25	0.3	0.65	0.7	0.25	0.2	0.15	0	0	0	125
29	6 mos.	14	M	0.1	0.2	0.1	0	0.1	0.35	0.45	1.15	1.1	0.2	0	0	?	0.4	0.3	135
30	6 mos.	5,320 Gm.	M	0.1	0.05	0	0	0	0	0.2	0.3	0.4	0.2	0.1	0.1	0	0.05	0.1	
31	8 mos.	15	F	0	0.05	0	0.1	0	0.08	0.4	0.3	0.3	0	0.3	0.1	0	0.2	0.1	135
32	8 mos.	18	F	0	0.05	0.01	0.1	0	0.05	0.5	0.3	0.4	0	0.3	0	0	0.15	0.05	
33	10 mos.	20	F	0.05	0.05	0.05	0	0	0.1	0.2	0.5	0.3	0.1	0.05	0	0.05	0.1	0.05	
34	11 mos.	19	F	0.1	0.1	0.05	0	0	0.05	0.6	0.7	0.3	0.15	0.3	0.2	0.2	0.3	0.05	110
35	11 mos.	17	F	0.09	0.1	0.09	0	0.1	0.15	0.3	0.6	0.7	0.35	0.3	0.25	0.15	0.1	0.09	180
36	11 mos.	17	F	0.1	0	0	0.1	0.1	0	0.55	0.8	0.25	0.2	0.3	0.2	0.2	0.25	0.1	110.5
37	11 mos.	19	F	0.15	0.2	0	0.1	0.25	0.1	0.4	0.1	0	0.2	0.3	0	0.15	0.25	0	120
38	13 mos.	21	F	0.05	0.1	0.15	0.1	0	0	0.8	0.7	0.4	0.2	0.25	0.1	0.2	0.25	0.2	135
39	14 mos.	18	M	0.1	0.2	0.05	0.15	0.4	0.5	1.0	1.2	1.0	0.1	0.1	0	0.6	0.5	0.2	140
40	14 mos.	22	M	0.1	0.1	0	0.1	0.3	0.4	1.1	1.7	1.0	0.1	0.35	0.15	0.3	0.2	0	105
41	15 mos.	22	M	0.1	0	0.05	0	0	0.2	0.4	0.4	0.8	0.2	0.05	0	0.2	0.1	0.1	105
42	16 mos.	24	M	0	0.1	0.1	0	0.2	0.2	0.35	0.9	0.7	0	0	0	0.1	0.15	0	135
43	19 mos.	27	M	0.1	0.1	0	0	0.1	0.2	0.45	0.7	0.4	0.2	0.2	0.1	0.2	0.15	0	145
44	19 mos.	29	F	0.2	0.2	0.1	0.1	0.2	0.2	1.0	0.7	0.6	0.2	0.2	0.2	0.3	0.3	0.2	110
45	1 year	20	M	0	0.1	0	0	0	0.1	0.5	1.0	0.55	0	0	0	0.2	0.25	0	115

TABLE 3.—Ten Normal Electrocardiograms of Children Aged from 2 Years to 5 Years Inclusive

No.	Age,	Weight, Lbs.	Sex	P			Q			R			S			T			Rate
				1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
1	2 years	24	M	0.1	0.1	0.05	0	0.05	0.1	0.4	0.7	0.5	0	0	0	0.1	0.2	0.1	160
2	2 years	19	M	0.1	0.15	0.1	0.1	0.2	0.1	0.4	0.75	0.55	0.15	0.2	0.05	0.1	0.2	0	187
3	3½ years	31	M	0.05	0.2	0.05	0.1	0	0	0.3	0.5	0.2	0.1	0.3	0.1	0.2	0.4	0.1	88
4	3½ years	32	F	0.04	0.05*	0.05	0.05	0.05	0	0.3	1.2	0.6	0.05	0.2	0.05	0.2	0.5	0.1	82
5	4 years	35	F	0.15	0.05	0.1	0.15	0.05	0.15	0.6	0.7	0.6	0	0.15	0	0.5	0.4	0.15*	75
6	4 years	36	M	0.1	0.15	0.05	0	0	0	0.6	1.2	0.6	0.2	0.4	0.2	0.3	0.4	0.1*	83
7	4½ years	36	F	0.1	0.3	0.2	0 1	0	0.05	0.4	0.6	0.4	0.4	0.2	0.1	0.3	0.3	0.15	100
8	5 years	47	F	0.15	0.2	0.1	0.1	0	0	0.5	0.6	0.2	0	0.1	0.4	0.4	0.6	0.3	82
9	5 years	49	M	0.1	0.3	0.1	0	0.1	?	0.7	0.7	?	0.3	0.4	0.2	0.3	0.4	?	105
10	5 years	40	F	0.1	0.2	0.1	0	0.1	0.05	0.7	0.8	0.5	0.1	0.2	0.3	0.2	0.2	0.3	94

TABLE 4.—Twenty-Six Electrocardiograms of Children Aged from 6 Years to 13 Years

No.	Age, Yrs.	Weight, Lbs.	Sex	P			Q			R			S			T			Rate
				1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
1	6	41	M	0.1	0.2	0.05	0	0	0	0.6	0.8	0	0.3	0.1	0.2	0.4	0.5	0.1*	97
2	6	47	M	0.15	0.25	0.15	0.1	0.1	0.05	0.7	1.1	0.4	0	0.1	0	0.4	0.4	0.2*	100
3	6	43	F	0.1	0.05	0.1*	0.05	0	0	0.6	0.8	0.2	0	0.2	0.15	0.4	0.3	0.3*	101
4	6	42	F	0.15	0.25	0.15	0	0.2	0.3	0.9	2.2	2.1	0.1	0.1	0	0.5	0.6	0.4	100
5	6	41	M	0.1	0.2	?	0	0	?	0.5	0.7	?	0	0	?	0.4	0.3	?	95
6	7	45	F	0.2	0.2	0.1	0.1	0	0.2	0.7	0.9	0.5	0.4	0.2	0	0.7	0.5	0.4	96
7	7	47	F	0.1	0.15	0.1	0	0	0.15	0.2	0.7	0.65	0.25	0.18	0.15	0.2	0.3	0.2	100
8	7	46	F	0.05	0.15	0.2	0	0	0	0.35	1.1	0.8	0.2	0.4	0.1	0.2	0.6	0.4	80
9	7	45	F	0.1	0.2	0.05*	0	0	0	0.8	1.1	0.4	0	0.2	0.5	0.5	0.9	0.2	101
10	8	49	F	0.1	0.08	0.1*	0	0	0.2	0.85	1.4	0.5	0.2	0.2	0.25	0.2	0.2	0.2*	80
11	8	49	F	0.1	0.2	0.15	0.1	0.1	0	0.5	1.3	0.9	0.1	0.3	0.2	0.3	0.4	0.2	96
12	8	50	M	0.15	0.2	0.1*	0	0.15	0.2	0.4	1.0	0.7	0	0.1	0	0.5	0.4	0.2*	96
13	9	58	M	0.1	0	0.1*	0.15	0	0	0.6	0.4	0.2	0.05	0.4	0.5	0.3	0.1	0.1*	82
14	10	61	M	0.1	0.15	0.15	0.1	0	0	0.5	1.2	0.9	0	0.2	0.1	0.3	0.6	0.15	80
15	10	65	M	0.1	0.3	0.1	0	0.1	0.1	0.5	1.2	0.6	0.1	0.4	0.3	0.3	0.9	0.1	88
16	10	68	M	0.15	0.1	0.1	0	0.1	0.2	1.0	1.2	0.5	0.2	0.4	0.2	0.5	0.6	0.3	100
17	11	64	M	0.1	0.1	0.1	0	0	0	0.4	0.8	0.4	0	0.05	0.1	0.3	0.4	0.1	90
18	11	68	M	0.15	0.1	0.1*	0.15	0	0	1.0	0.5	0.1	0.1	0.2	0.3	0.4	0.2	0.1*	80
19	11	74	M	0.1	0.15	0.1	0	0	0	0.5	0.95	0.8	0.2	0.2	0.1	0.2	0.2	0.2	113
20	11	70	M	0.05	0.2	0.1	0	0.2	0.2	0.35	1.4	0.9	0.2	0	0	0.1	0.3	0.1	110
21	11	71	F	0.1	0.1	0.05	0	0	0.02	0.6	0.75	0.4	0	0	0	0.1	0.2	0.05	82
22	12	78	M	0.1	0.15	0.1	0.1	0	0.1	0.8	1.2	0.6	0.2	0.5	0.2	0.4	0.5	0.1	108
23	13	84	M	0.1	0.2	0	0	0	0	0.9	1.6	0.7	0	0	0	0.4	0.4	0.1	100
24	13	72	M	0.05	0.2	0.1	0	0.05	0.1	0.45	1.2	1.3	0.2	0.2	0.1	0.3	0.4	0.15	108
25	13	96	M	0.2	0.2	0.10	0.1	0.05	0	1.6	1.6	0.9	0.3	0.2	0.1	0.4	0.3	0.15	95
26	13	84	M	0.1	0.1	0.05	0	0	0	0.4	0.4	0.2	0.2	0.3	0.1	0.4	0.1	0.1*	78

TABLE 5.—Pulse Period and Rate of Normal New-Borns

No.	Age	Sex	Weight, Gm.	Pulse Period	Smallest	Largest	Arithmetical Average	Difference	Pulse Rate
1	24 hours	M	3,600	15–15–15–15–15 15–15–15–15–15	15	15	15.0	0	210
2	24 hours	F	2,840	20–20–20–22–20 24–22–20–22–20	20	24	21.0	4	152
3	2 days	M	3,230	35–33–33–30–29 29–29–28	28	35	30.6	7	102
4	2 days	F	2,940	19–20–20–20–20 20–21–21	19	21	20.1	2	159
5	3 days	M	3,250	20–20–19–20–21 20	19	21	16.6	2	158
6	6 days	F	3,440	17–17–17–17–17 17–18–18–18–17	17	18	17.3	1	180
7	5 days	M	3,420	15–15–15–15–15 15–15–15–15–15	15	15	15.0	0	210
8	4 days	M	3,810	19–20–18–18–18 19–18–19–19–19	18	20	18.7	2	158
9	6 days	F	3,440	22–24–23–23–23 24–24–23	22	24	23.2	2	150
10	7 days	F	4,000	23–23–24–25–24 24–24–24	23	25	23.8	2	132
11	7 days	F	3,115	27–25–28–27–27	25	28	26.8	3	118
12	7 days	M	3,430	18–18–18–18–18 18–18–19–18–18	18	19	18.1	1	160
13	11 days	M	3,545	20–19–20–20–19	19	20	19.6	1	158
14	9 days	M	3,900	23–24–25–24–23 23–23–24–25–24	23	25	23.8	2	135
15	9 days	M	3,900	17–18–17–18–18 17–18–17–17–18	17	18	17.5	1	180

Average pulse rate, 157.
Average pulse period, 20.4 (in 1/50 second).
Average difference between highest and lowest pulse period, 1.0 (in 1/50 second).

TABLE 7.—Pulse Period and Rate of Normal Children Aged from 2 to 5 Years

No.	Age	Sex	Weight, Lbs.	Pulse Period	Smallest	Largest	Arithmetical Average	Difference	Pulse Rate
1	13 mos.	M	21	24–22.5–22.5–21–21–20.5 20.5–20.5–20.5–22.5	20.5	24.0	21.5	4.0	144
2	14 mos.	M	24	31–29–28–30–30–30	28.0	31.0	29.6	3.0	105
3	14 mos.	M	26	22–22–22–22–22–22–22 22–22–22	22.0	22.0	22.0	0	135
4	15 mos.	F	22	28–28–28–28–28–28–27.5 27.5–27.5–26.5	26.5	28.0	27.7	1.5	108
5	15 mos.	F	23	24.5–25.5–25.5–26–27.5 29–25.5–29–29	24.5	29.0	26.6	4.5	108
6	16 mos.	F	24	25–24–29–29–22.5–22.5 22.5–23–24–24	22.5	25.0	23.5	2.5	135
7	19 mos.	F	27	20–20–20–20–20–20–20 20–20–20.5	20.0	20.5	20.0	0.5	145
8	2 years	F	28	15.5–15.5–15.5–15.5–15.5 15.5–15.5–15.5–15.5	15.5	15.5	15.5	0	190
9	2 years	F	26	20–20.5–20–20–20–20.5 20.5–20.5	20.0	20.5	20.3	0.5	120
10	2 years	F	25	21–21–21–21–21–21–21 21–21–20	20.0	21.0	20.9	1.0	144

Average pulse rate, 133.
Average pulse period, 22.7 (in 1/50 second).
Average difference between highest and lowest pulse period, 1.75 (in 1/50 second).

TABLE 6.—Pulse Period and Rate of Normal Nurslings Aged from 11 Days to 1 Year

No.	Age	Sex	Weight, Gm.	Pulse Period	Smallest	Largest	Arithmetical Average	Difference	Pulse Rate
1	6 weeks	M	4,200	19.5–19.5–19.5–19.5–19.5 19.5–19.5–19.5–19.5	19.5	19.5	19.5	0	132
2	6 weeks	M	3,900	21–21–21–22.5–21–21 20–20–20	20.0	22.5	20.8	2.5	144
3	6 weeks	M	4,120	18.7–18.7–18.7–18.7–18.7 18.7–18.7–18.7–18.7–18.7	18.7	18.7	18.7	0	165
4	6 weeks	F	4,100	22.5–23–20.5–21.5–21.5 20.5–22–22–22–24	21.5	24.0	22.0	2.5	144
5	7 weeks	M	4,230	19–19–19–19–19–19–20 20–20–20	19.0	20.0	19.4	1.0	150
6	2 mos.	F	4,330	24–24–24–24–24–24–24 24–24–25	24.0	25.0	24.1	1.0	120
7	2 mos.	F	4,500	26–25.5–25.5–25–25–25 25–23.5	23.5	26.0	25.0	2.5	125
8	2 mos.	M	4,120	23–23–23–23–23	23.0	23.0	23.0	0	135
9	2 mos.	M	4,020	16–16–16–16–16–16–16 16–16–16	16.0	16.0	16.0	0	182
10	7 weeks	F	4,230	20–20–20–20–20–20–20.5 20–20–20	20.0	20.5	20.0	0.5	145
11	74 days	M	3,720	19–20–20–20–20–21.5–24 24–24	19.0	24.0	23.7	5.0	144
12	8 mos.	M	8,100	23.5–23.5–23.5–23.5–23.5 23.5–23.5–23–23–23	23.0	23.5	23.4	0.5	128
13	.....	..	.....	20.5–20.5–20.5–20.5–20.5 20.5–20.5–20.5–20.5–20.5	20.5	20.5	20.5	0	145
14	10 mos.	F	9,000	20–20.5–20.5–20.5–20.5 20.5–20.5–21–21–21	20.5	21.0	20.6	0.5	150
15	11 mos.	M	8,560	26–26–26–26–23.5–28.5 28.5	26.0	28.5	27.0	2.5	117
16	11 mos.	F	8,900	24–24–24–24–24–24–24 24–24–25	24.0	25.0	24.1	1.0	135
17	3½ mos.	F	5,850	24–23–23–23–23–23–24	23.0	24.0	23.2	1.0	132
18	4 mos.	F	6,120	26–26–26–26–26–26–26 26–26	26.0	26.0	26.0	0	118
19	5 mos.	M	4,220	21.5–21.5–21.5–21.5–21.5 21.5–21.5–21.5	21.5	21.5	21.5	0	135
20	5½ mos.	M	4,800	30–29.5–29.5–29.5–29.5 29.5	29.5	30.0	29.6	0.5	126
21	6 mos.	M	5,100	24–22.5–22.5–22.5–22.5–22.5 22.5–22.5–22.5–22.5	22.5	24.0	22.8	1.5	135
22	11 mos.	F	7,650	19–18.8–18.8–18.8–18.8–18.8 18.8–19.5–19.5–19.5	18.8	19.5	19.0	0.7	168
23	11 mos.	F	8,345	27–27–27–27–27–27–27–28.5	27.0	28.5	27.2	1.5	108

Average pulse period, 22.5 (in 1/50 second).
Average pulse rate, 138.
Average difference between highest and lowest pulse period, 1.0 (in 1/50 second).

TABLE 8.—Pulse Period and Rate of Normal Children Aged from 6 to 13 Years

No.	Age	Sex	Weight, Lbs.	Pulse Period	Smallest	Largest	Arithmetical Average	Difference	Pulse Rate
1	3½ years	M	35	35–31.5–31.5–33.5–33.5 32–30–31	30.0	35.0	32.2	5.0	85
2	4½ years	M	38	35.5–37–37.5–37	35.5	37.5	36.6	2.0	84
3	6 years	F	42	33.8–32–20–28–28–30–30	28.0	33.8	30.2	5.8	105
4	6 years	M	44	31–30–31.6–33–33–32	30.0	33.0	31.7	3.0	96
5	6 years	F	39	33–36–32–31–30–34–34 34–35	30.0	36.0	33.1	6.0	105
6	6 years	F	37	40–35–31–32–35.5–35.5	31.0	40.0	34.8	9.0	84
7	7 years	M	44	39–40.5–37.5–39–35.5	35.5	40.5	38.5	5.0	82
8	7 years	M	45	33–33–33–33–34–34–33 33–33–33	33.0	34.0	33.2	1.0	96
9	7 years	M	47	34–35–35–41–40–40.5	34.0	41.0	37.6	7.0	84
10	7 years	F	46	32.5–29.5–30.5–34–34 30.5	29.5	34.0	31.7	4.5	96
11	8 years	F	51	36–37.5–37.5–37.5–37.5–37.5 37.5–35.5–37.5–37.5	35.5	37.5	37.1	2.0	99
12	11 years	F	75	27.5–27.5–27.5–27.5–27.5 27.5	27.5	27.5	27.5	0	108
13	8 years	F	50	42–39–42–36.5–44–44.5	36.5	44.5	41.3	8.0	75
14	9 years	M	59	29–31–34–33–30–31.5–37 30.5	29.0	37.0	32.0	8.0	96
15	11 years	M	78	26.5–26.5–26.5–26–26–26	26.0	26.5	26.3	0.5	108
16	11 years	M	76	36–35–36–34.5	34.5	36.0	35.4	1.5	84
17	11 years	M	68	25.5–25.5–25.5–25.5–25.5 26.5–26.5–29–29.5	25.5	29.5	26.5	4.0	115
18	13 years	F	85	29–28–28–28–28–28–28	28.0	29.0	28.1	1.0	108
19	13 years	F	81	30.5–39–35–31.5–31.5–31–35	30.5	39.0	33.3	8.5	80

Average pulse rate, 83.6.
Average pulse period, 33.0 (in 1/50 second).
Average difference between highest and lowest pulse period, 4.3 (in 1/50 second).

TABLE 9.—Transmission Time of Normal New-Borns

No.	Age	F R	R T	T P	P P	Percentage			Pulse Rate
						P R to P P	R T to P P	T P to P P	
1	10 days	0.10	0.23	0.27	0.60	16.6	38.33	45.0	100
2	2 days	0.111	0.21	0.08	0.40	27.5	52.50	20.0	150
3	16 hours	0.12	0.20	0.05	0.37	23.4	54.05	13.5	157
4	24 hours	0.112	0.23	0.05	0.40	30.0	57.5	12.5	152
5	4 days	0.15	0.22	0.08	0.45	33.3	48.88	17.5	135
6	9 days	0.12	0.20	0.03	0.35	34.3	57.14	8.57	174
7	18 hours	0.11	0.19	0.10	0.40	27.5	47.5	25.0	150
8	5 days	0.10	0.21	0.10	0.41	24.3	51.22	24.19	135
9	3 days	0.09	0.21	0.09	0.39	23.3	53.85	23.33	150
Average.....		0.113	0.211	0.94	0.419	27.7	50.07	21.10	144.8
Average percentage calculated from the averages.....						26.9	50.36	22.43	

TABLE 10.—Transmission Time of Normal Nurslings Aged from 11 Days to 1 Year

No.	Age	PQ	QRS	ST	TP	PP	Percentage				Pulse Rate
							PR to PP	QRS to PP	ST to PP	TP to PP	
1	4 wks.	0.11	0.03	0.19	0.03	0.36	30.5	8.40	52.77	8.33	164
2	6 wks.	0.13	0.03	0.22	0.07	0.45	28.9	6.67	48.88	15.55	144
3	6 wks.	0.10	0.04	0.21	0.09	0.44	22.7	9.45	47.73	20.45	144
4	6 wks.	0.12	0.04	0.19	0.05	0.40	35.1	4.9	47.5	12.50	157
5	6 wks.	0.12	0.03	0.20	0.05	0.40	32.5	5.00	50.0	12.5	157
6	7 wks.	0.11	0.03	0.21	0.05	0.40	27.5	7.50	52.5	12.5	150
7	11 mos.	0.13	0.04	0.20	0.07	0.42	30.9	4.91	47.62	16.57	135
8	2 mos.	0.12	0.04	0.20	0.08	0.43	27.9	6.99	46.51	18.60	140
9	2 mos.	0.11	0.02	0.18	0.04	0.35	31.4	5.76	51.42	11.42	180
10	4 mos.	0.12	0.02	0.22	0.11	0.47	25.5	4.30	46.8	23.40	132
11	5 mos.	0.15	0.03	0.24	0.04	0.46	32.6	6.54	52.17	8.69	135
12	5½ mos.	0.12	0.04	0.21	0.09	0.48	25.0	12.50	43.75	18.75	126
13	6 mos.	0.13	0.05	0.21	0.04	0.43	30.2	11.67	48.83	9.30	135
14	8 mos.	0.12	0.02	0.21	0.13	0.48	25.0	4.17	43.75	27.08	126
15	10 mos.	0.12	0.04	0.24	0.05	0.45	26.6	8.96	53.33	11.11	135
16	11 mos.	0.18	0.05	0.22	0.10	0.55	38.9	2.92	40.00	18.18	98
17	11 mos.	0.14	0.05	0.27	0.06	0.52	26.9	9.64	51.92	11.54	117
18	14 mos.	0.12	0.04	0.18	0.06	0.40	30.0	10.00	45.00	15.0	150
Average...		0.125	0.036	0.211	0.067	0.44	29.34	7.24	48.36	15.19	133.3
Average percentage calculated from the averages..							28.0	8.18	47.28	15.22	

TABLE 11.—Transmission Time of Normal Children Aged from 1 Year to 5 Years

No.	Age	PQ	QRS	ST	TP	PP	Percentage				Pulse Rate
							PR to PP	QRS to PP	ST to PP	TP to PP	
1	13 mos.	0.11	0.04	0.20	0.10	0.45	24.44	8.88	44.44	22.22	135
2	12 mos.	0.11	0.04	0.22	0.11	0.48	22.91	8.33	45.81	22.91	132
3	12 mos.	0.10	0.04	0.22	0.22	0.58	17.24	6.89	37.93	37.93	105
4	14 mos.	0.11	0.07	0.20	0.08	0.46	23.93	15.21	43.47	17.38	135
5	15 mos.	0.12	0.04	0.22	0.20	0.58	20.69	6.89	37.93	34.48	108
6	15 mos.	0.11	0.05	0.25	0.11	0.52	21.15	9.61	48.07	21.15	108
7	16 mos.	0.13	0.04	0.20	0.08	0.45	28.88	8.88	44.44	17.77	135
8	19 mos.	0.11	0.04	0.20	0.20	0.55	20.0	7.27	36.36	36.36	108
9	19 mos.	0.11	0.06	0.20	0.03	0.40	27.5	15.0	50.0	17.5	145
10	2 yrs.	0.12	0.04	0.18	0.08	0.42	28.57	9.52	61.94	19.45	142
11	2 yrs.	0.11	0.06	0.17	0.05	0.39	28.20	15.38	43.59	12.82	158
12	2 yrs.	0.16	0.035	0.22	0.08	0.49	32.65	7.14	44.89	16.32	119
13	3½ yrs.	0.16	0.07	0.23	0.18	0.64	25.0	10.93	35.93	28.12	95
14	4½ yrs.	0.16	0.07	0.28	0.22	0.73	21.92	9.59	38.35	30.13	88
Average...		0.123	0.049	0.213	0.125	0.51	24.50	9.97	43.79	23.19	122.3
Average percentage calculated from the averages..							24.11	9.61	41.76	24.51	

TABLE 12.—Transmission Time of Normal Children Aged from 6 to 13 Years

No.	Age	PQ	QRS	ST	TP	PP	Percentage				Pulse Rate
							PR to PP	QRS to PP	ST to PP	TP to PP	
1	6 yrs.	0.12	0.04	0.28	0.11	0.55	21.8	7.27	50.9	20.0	108
2	6 yrs.	0.14	0.06	0.26	0.14	0.60	23.3	10.0	43.3	23.3	100
3	6 yrs.	0.13	0.07	0.30	0.17	0.67	19.4	10.4	44.7	25.3	90
4	7 yrs.	0.16	0.08	0.31	0.18	0.73	21.9	10.9	41.6	24.7	82
5	7 yrs.	0.18	0.08	0.26	0.12	0.64	28.1	12.5	40.6	18.7	95
6	7 yrs.	0.16	0.06	0.26	0.12	0.60	26.6	10.0	43.3	20.0	96
7	7 yrs.	0.14	0.07	0.27	0.09	0.57	24.5	12.2	47.3	15.7	100
8	8 yrs.	0.12	0.08	0.28	0.30	0.78	15.3	10.2	36.2	38.4	72
9	8 yrs.	0.11	0.08	0.28	0.26	0.73	15.0	10.9	38.3	35.6	80
10	9 yrs.	0.12	0.06	0.27	0.22	0.67	17.9	8.9	40.2	35.8	95
11	10 yrs.	0.12	0.07	0.29	0.06	0.54	22.2	12.9	53.5	11.1	105
12	10 yrs.	0.11	0.06	0.29	0.20	0.66	16.6	9.0	43.9	30.3	90
13	11 yrs.	0.14	0.06	0.24	0.07	0.51	27.4	11.7	47.0	13.7	110
14	11 yrs.	0.12	0.08	0.26	0.05	0.51	23.5	15.6	50.9	9.8	112
15	11 yrs.	0.18	0.08	0.26	0.18	0.70	25.7	11.4	37.1	25.7	84
16	12 yrs.	0.15	0.06	0.27	0.06	0.54	27.7	11.1	50.0	11.1	108
17	13 yrs.	0.13	0.08	0.24	0.09	0.54	24.0	14.8	44.4	16.6	108
18	13 yrs.	0.17	0.08	0.30	0.08	0.63	26.9	12.6	47.6	12.6	95
Average...		0.138	0.069	0.273	0.139	0.620	22.6	11.2	44.4	21.5	961
Average percentage calculated from the averages..							22.25	11.13	44.03	22.41	

TABLE 13.—Weight of the Musculature of the Left and Right Ventricles in Grams

Boys		Girls		Age	Boys: L.R. Index	Girls: L.R. Index
Left	Right	Left	Right			
3.51	3.8	.....	.....	Fetus 8 mos.	0.92	
5.04	4.35	4.33	3.62	Fetus 9 mos.	1.1	1.1
8.14	6.54	7.95	6.47	Newborn.....	1.2	1.2
12.07	7.23	10.92	6.81	1 to 2 mos.	1.7	1.6
18.13	9.13	16.72	8.61	5 to 6 mos.	2.0	2.0
24.48	12.47	23.49	11.82	11 to 12 mos.	2.0	2.11
29.29	15.92	28.15	14.65	1 to 2 years.....	1.84	1.92
38.51	18.16	36.25	17.69	3 to 4 years.....	2.12	2.05
44.98	23.48	43.07	20.24	5 to 6 years.....	1.97	2.13
49.94	23.33	45.83	23.39	6 to 7 years.....	2.14	1.95
52.25	25.08	48.36	23.39	7 to 8 years.....	2.08	2.06
54.29	26.62	50.76	24.72	8 to 9 years.....	2.04	2.07
57.74	27.7	50.51	26.62	9 to 10 years.....	2.08	1.97
60.39	30.12	59.83	28.54	10 to 11 years.....	2.04	2.10
66.98	32.21	67.3	33.92	11 to 12 years.....	2.79	1.99
72.87	38.0	73.1	36.98	12 to 13 years.....	1.92	1.98
95.45	41.76	93.2	43.7	13 to 14 years.....	2.04	2.13

TABLE 14.—Thickness of the Walls of the Right and Left Ventricles

Author	Age	Right Ventricle	Left Ventricle	L.R. Index
Bednar.....	Fetus 3 mos.	1.5	1.0	0.66
Bednar.....	Fetus 6 mos.	4.0	3.0	0.75
Bednar.....	Birth	0.44–0.68	0.34–0.44	0.75–0.65
Bednar.....	Newborn	4.0	4.0	1.0
Falk.....	Newborn	0.27	0.42	1.55
Gillepsie.....	Newborn	4.0	3.0	0.75
Gillepsie.....	Newborn	5.0	5.0	1.0
Gibson.....	Newborn	4.0	4.0	1.0
Bednar.....	1 month	3.2	5.4	1.68
Gibson.....	1 month	3.2	5.4	1.68
Gibson.....	2–3 months	2.6	6.0	2.31
Gibson.....	4–5 months	3.0	6.5	2.17
Bednar.....	5 months	3.0	6.5	2.17
Falk.....	5–6 months	2.7	5.2	1.92
Gibson.....	6–8 months	2.3	6.8	2.95
Gillepsie.....	11 months	2.0	5.0	2.5
Gibson.....	9–12 months	3.4	8.1	2.38
Gillepsie.....	22 months	2.0	8.0	4.0
Notori.....	2–9 years	3.4–8.1	8.1	2.38
Notori.....	10–20 years	4.0	1.0	2.50

again an increase similar to that after the fourth year. In this lead the average for the first two years is .9 mm., and the average from the second year to the thirteenth year is 3.4 mm. The average for the adult, according to Lewis, is 2 mm.

In Lead II the T deflection is on the whole higher than in Lead I. It is inconstant from month to month, thus being valueless as a guide for the normal. The average of T_2 up to the second year is 1.4 mm. and during the rest of childhood 3.5 mm.

T_3 is still more variable. The average for the first two years is one scale division, for the rest of childhood two scale divisions. The average of T_3 for the adult (according to Lewis) is 1.6 mm.

I believe that the height of the T-wave is too variable to be used as a standard. It is too easily affected by all external influences. If

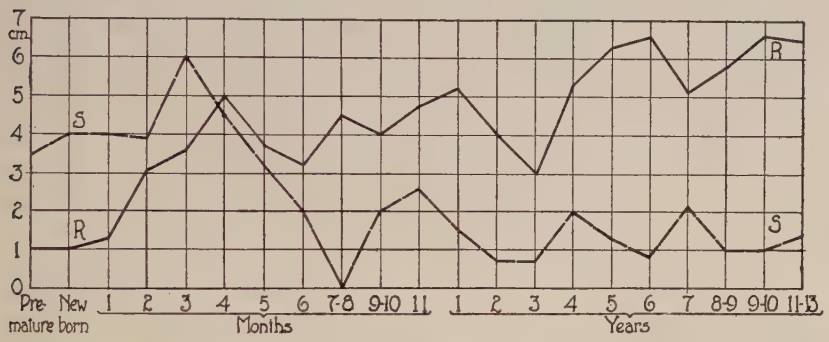

FIG. 85.—Comparison of R_1 and S_1 in all ages. Each square represents 0.5 mvlt. or 5 scale divisions.

a baby cried before being cardiographed, or for a moment during the experiment, even though this moment was without influence on the other deflections, it usually affected T. This is probably the most plausible reason for the high peaks seen in Figs. 83, 84, at periods where there are no physiological causes; *e.g.*, in Lead I at four months and at one year, in Lead II at three months and at seven years, in Lead III at three months and at six years.

The T-wave was rather rarely inverted. It was normal in all leads at all ages, except in Lead III between the ages of 6 and 13, during which period it was inverted in 15 per cent. of the cases (Fig. 85).

Rate and Rhythm.—Many pediatrists believe that the pulse of the normal child is more susceptible to changes in rate and rhythm than the pulse of the adult and that this is especially true of the newborn and infant. Further, the pulse is so variable that it is difficult to establish a normal standard, and arrythmias are said to occur much more frequently in the newborn and the nursling than in later childhood. My own studies of electrocardiographic tracings of hearts of normal children do not confirm this opinion. On the contrary, I find that the younger the child the faster his pulse rate and the faster the pulse rate the less frequent

arrhythmias. The fact that the nurslings were fed before the reading might account for the rather high pulse rates shown in Tables 5 to 8. From each tracing the average of 7 to 10 pulse periods was taken. The time interval for each pulse period was recorded in fiftieths of a second.

Following Krumbhaar, irregularities showing a difference of more than .1 second between the shortest and longest heart cycle, were considered evidence of a sinus arrhythmia. In lowest pulse periods the average difference between the highest and lowest pulse periods .04 second. (Hecht and Krumbhaar state as average difference .12 and .04 second respectively. From 6 to 13 years the figures of Hecht and Krumbhara are .16 and .10 second respectively.)

Although there is a slight difference in the exact time interval in the three studies mentioned, the impression that arrhythmias are more frequent in newborns than in older children is upheld by all. In general the pulse rate decreases with age, and arrhythmias become more frequent. In the newborn, I find only one case of sinus arrhythmia with a difference of .14 second (Table 5 No. 3). In the next group (11 days to 1 year) the highest irregularity is .10 second (Table 6). In the next group (1 to 5 years), there is only one instance with a difference of .08 second (Table 7). In school children however (6 to 13 years), 47 per cent. show an arrhythmia over .10 second (Table 8).

Transmission Time.—In order to interpret correctly an electrocardiogram, one must first know what constitutes the normal variations in the auricular and ventricular condition time in children of all ages. To establish a normal standard, I measured the P-R interval (auricular activity), the R-T interval (ventricular activity), which includes the Q-R-S and S-T intervals, the T-P interval (diastolic phase) and the P-P interval representing the complete heart cycle. I then calculated the ratio in the percentages between the three phases of the heart cycle, the P-R, the R-T, the T-P, and the entire heart cycle, the P-P.

P-R Interval.—In the newborn the auricular impulse is shorter than at any later period. It shows a remarkable constancy averaging .113 second. The longest period is .15 second, and the shortest .09 second. The average obtained from the percentages calculated from each of the tracings is 27.7 per cent. The average obtained from these averages is 26.91, a difference of about 1 per cent. (Table 9).

In the next period (from 11 days to 1 year) the P–R interval averages slightly more, .125 second. The shortest period is .10 second and the longest .18 second. The P-R ratio is 29.34 per cent. and 28 per cent. respectively (Table 10). From the first to the fifth year the P-R interval is slightly less than in the previous period, .123 second, the lowest being .10 second and the highest .16 second. The auricular impulse at this age constitutes from 24.11 to 24.50 per cent. of the entire heart cycle (Table 11).

In the last period of childhood (6 to 13 years) the P-R interval averages .138 second. The shortest and the longest intervals are .11 second and .18 second respectively. The conduction time is from 22.25 to 22.6 per cent. of the entire pulse period (Table 12).

R-T Interval.—The R-T interval is composed of the Q-R-S and the S-T periods. The Q-R-S is measured from the beginning of Q, if present, to the end of S, the S-T from the end of S to the end of T. On account of the frequent absence of Q in the newborn the R-T was calculated instead. During the first 10 days of life the period of ventricular activity thus determined amounts to from 50.07 to 50.36 per cent. of the heart cycle (a little less than twice the auricular activity). It measures .211 second, the lowest and the highest being .19 and .23 second respectively (Table 9). In the next period (11 days to 1 year) the R-T phase is somewhat longer. Both the Q-R-S and S-T can be recognized, the Q-R-S averaging .036 second, the S-T .211 second, thus making R-T .247 second (the minimum Q-R-S being .02 second, the maximum .05 second). The R-T interval is quite constant in all readings. The S-T averages .211 second. (The shortest and the longest intervals are .18 and .24 second respectively.) The Q-R-S : P-P ratio is 7.24 to 8.18 per cent. and the S-T : P-P ratio is 47.28 to 48.36 per cent. (Table 10).

In the next period (one to five years) the Q-R-S interval averages .049 second ranging from .035 to .07 second. It comprises from 9.61 to 9.97 per cent. of the entire heart cycle.

The S-T averages .213 second with a range of from .17 to .28 second. It is from 41.76 to 43.79 per cent. of the pulse period. The total Q-T interval during this period averages .262 and is about 51 per cent. of the pulse period (Table 11).

During the latter part of childhood the Q-S interval averages .069 second, ranging from .04 to .08 second. The S-T averages .273 second, ranging from .24 to .31 second. The Q-R-S : P-P ratio is 11.2 per cent., and the S-T : P-P ratio is 44.2 per cent. The total Q-T interval averages .342 second and the total Q-T : P-P ratio is 55 per cent. The average Q-T in the adult is .36 second (Q-R-S = .10 second) and (S-T = .26 second) (Table 12). With the exception of the S-T during the latter part of childhood, the duration of both the auricular and ventricular conduction time is less than in the adult.

T-P Interval.—The T-P interval represents the period of rest. It obviously depends upon the pulse rate. It is so variable and inconstant that it is useless as a guide for the normal.

Ventricular Preponderance.—Lewis defines ventricular preponderance as the disturbed weight ratio between the two ventricles. This may be due to pathological changes as in heart disease, or it may be entirely an physiological phenomenon as in the normal growth of the heart during and through childhood. In many instances, particularly in the infant, it is difficult to decide clinically whether a hypertrophy exists. In such an instance the electrocardiograph is especially valuable.

Figure 79 (taken from Lewis) is a schematic diagram of the separate curves of each ventricular phase in each lead. In the upper curve (*L*) the right division of the bundle which transmits impulses through the ventricle is severed below its origin, thus forcing the normal impulse to spread itself through the left branch. Lewis terms this the levogram.

The middle curve (*D*), called the dextrogram, represents the opposite condition. The left ventricle branch being severed the impulse

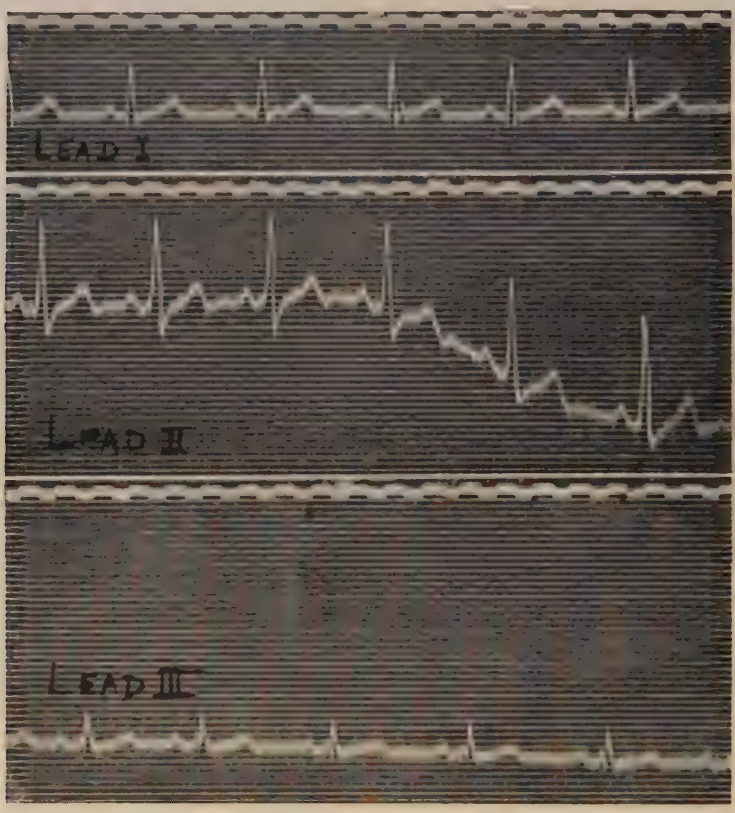

FIG. 86.—Effect of change of position on electrocardiogram. Patient lying on right side.

passes only through the right ventricle branch. The third curve, "bigram," represents the algebraic sum of the two.

All observers are agreed that in the premature, in the newborn, and during earliest infancy there is a definite and characteristic electrocardiogram, entirely different in form and height of deflection from that of the older child and the adult. Funaro, in 1908, under the direction of Nicolai, first observed this cardiogram, and concluded that it represented a left ventricular preponderance. The anatomical data in our possession at the present time contradict this opinion. Heubner, Noeggerath and others also noted this peculiar type of curve in the

newborn. Their explanation was based on the high position of the diaphragm and the more horizontal axis of the heart. This theory is not confirmed by the electrocardiograms which I obtained from subjects lying either on their left or right sides. In these instances, only the height of the deflections changed in the

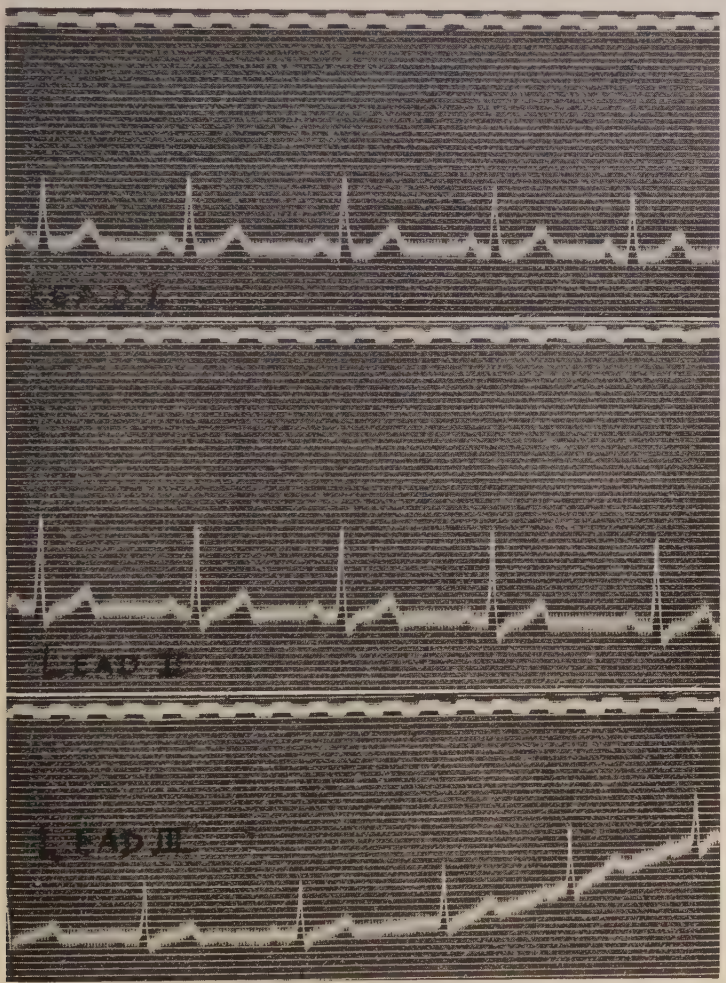

Fig. 87.—Effect on electrocardiogram of change of position. Patient seated.

different positions, the outline of the curve remained essentially the same (Figs. 86–89).

The question arises: What is the effect of the muscle mass, the thickness of the walls, and the weight of the ventricle on the electrocardiogram. A careful study (Tables 13 and 14) of the anatomical data obtained from dissections of hearts of children of all ages shows

the presence of a definite right ventricular preponderance in the newborn and during the first two to three months; whereas in the adult the left ventricle weighs from 1.8 (Lewis) to 2.6 (Pfaundler) as much as the right ventricle, in the newborn the two ventricles are about equal. At birth the walls of the right ventricle are of about the same thickness, (slightly less), as those of the left ventricle. In other words, the L/R index of the thickness of the walls is from .66 to 1.0 and the L/R

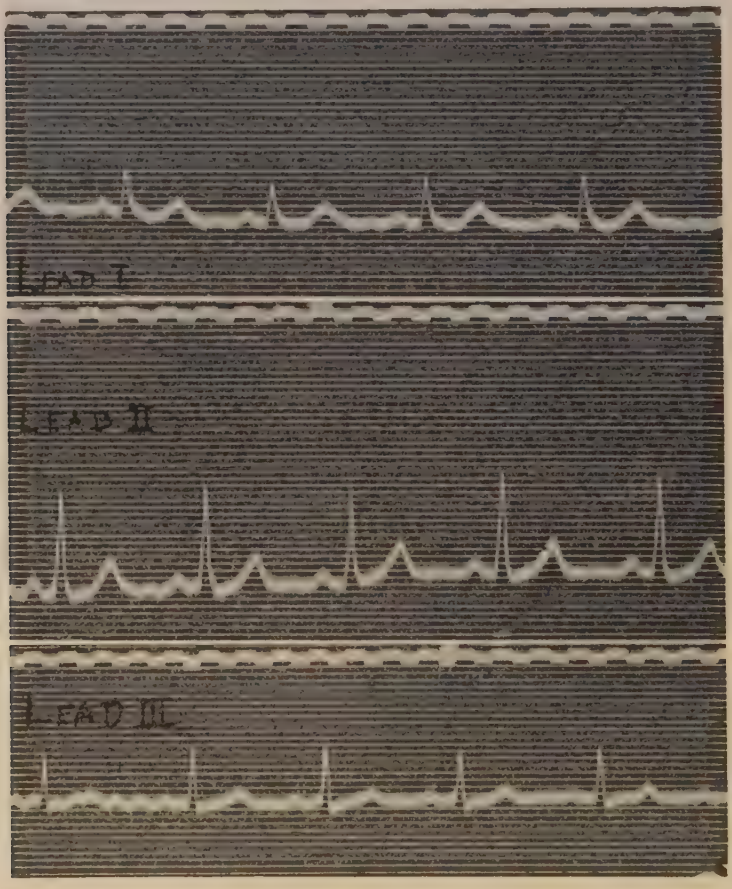

FIG. 88.—Effect on electrocardiogram of change of position. Patient recumbent.

index of the weight is approximately 1.0. It should be mentioned, however, that these anatomical figures are not entirely criticism proof: first, because of insufficient material; secondly, because the measurements have been taken by different authors at different levels of the heart; and thirdly, because some of the cases reported are probably still-births, which fact presupposes disease or prematurity.

Taking the adult electrocardiogram as a standard for comparison, it can be seen why the electrocardiogram of the newborn shows a right ventricular preponderance. In the curve of the newborn this is

exaggerated in Lead I and smaller in Lead III. R has very little or no amplitude in Lead I and is highest in Lead III. Q in Lead II and III is higher at this age than in the adult (Figs. 90–95).

Conclusions.—(1) In the premature and during the first three months of life, the normal electrocardiogram indicates a right ventricular preponderance. At about the fourth month R_1 becomes

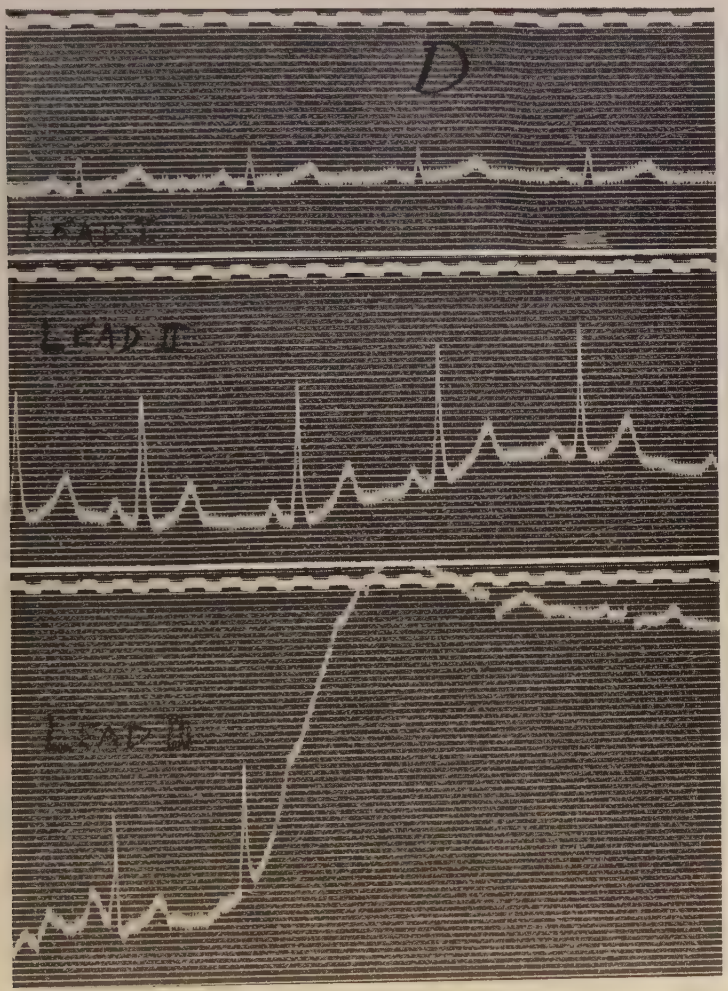

Fig. 89.—Effect of change of position on electrocardiogram. Patient lying on left side.

larger than S_1, and from then on the ventricular complex approaches the adult type of curve.

2. The average heights of the deflections in childhood are in general greater than in the adult.

3. Except in the premature, satisfactory records showing all the deflections present in the normal adult electrocardiogram can be obtained during any period of childhood.

4. In all three leads P is higher in childhood than in the adult. With the exception of the electrocardiogram of the permature, it was absent in the above series in only two instances. It was found electronegative in eight records.

5. The Q plays a prominent part in the electrocardiogram of childhood. It is larger than in the adult especially in Leads II and III. This adds confirmatory evidence that there is a right ventricular preponderance in the first few months of life.

6. During the first few months of life R in Lead I is lower than at any other period, but in Leads II and III it averages higher than in

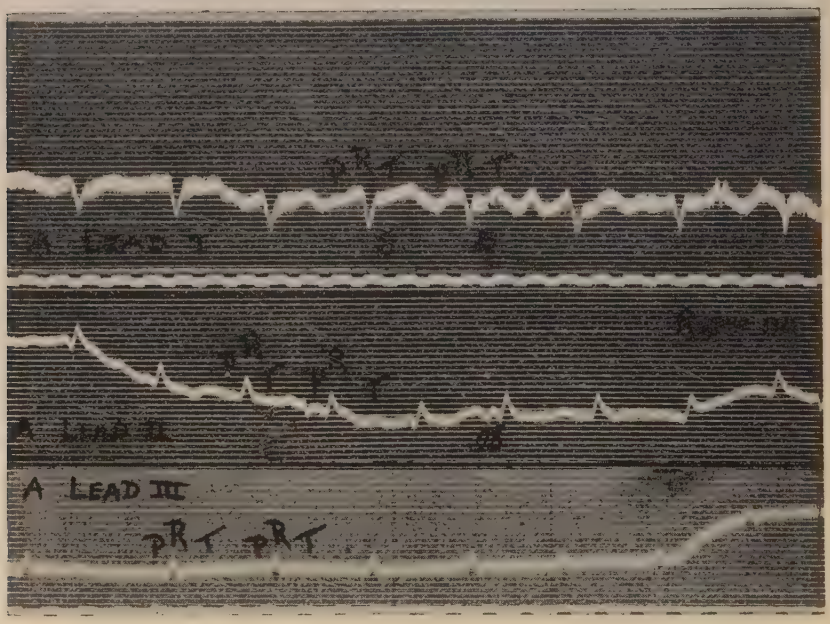

FIG. 90.—Electrocardiogram of a newborn four hours old.

the adult. The increase of R_1 and the decrease of S_1 are both indicative of a right ventricular preponderance during the earliest periods of life.

7. The S deflection is the most characteristic and distinctive of the ventricular complex in childhood. In Lead I it is relatively and absolutely higher in the first three months than in any other period of life and in the other leads it is relatively higher than in the adult.

8. In the child T is very susceptible to external influences and therefore its height is unreliable. In the first 10 days of life it is frequently absent. After that period it is quite constant. It was found inverted during the latter part of childhood in only 15 per cent. of the readings.

9. The general impression that the younger the child the more frequent the arrhythmias is not confirmed by the electrocardiograph. The younger the child the faster the pulse; and the faster the pulse the

less frequent arrhythmias. In the newborn the average difference between the highest and lowest pulse periods was $\frac{2}{50}$ second whereas in the older children (from 6 to 13 years) the average difference was $\frac{4.3}{50}$ second. In the period of infancy no sinus arrhythmia occurred (difference of a tenth of a second or more) while in the school age 47 per cent. showed sinus arrhythmias.

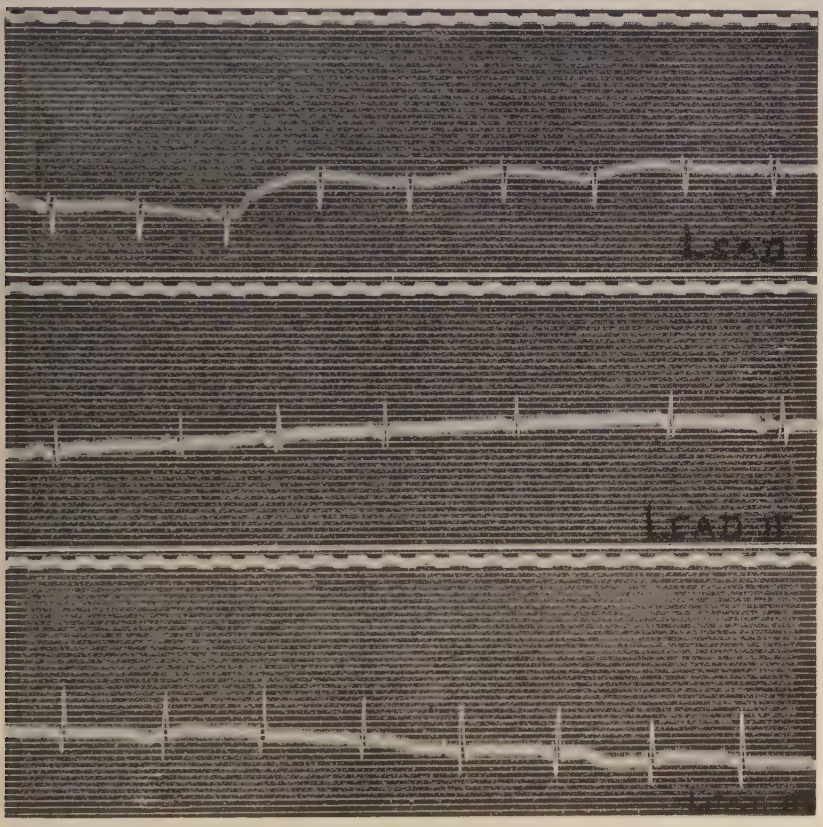

FIG. 91.—Electrocardiogram of normal newborn 24 hours old.

10. The transmission time in children is on the whole of shorter duration than in the adult. In the newborn the auricular activity assumes an average of .113 second, whereas in the last period of childhood the average amounts to .138 second. In the adult the P-R interval averages .18 second.

11. The ventricular conduction time in the child corresponds to the auricular. In the newborn it averages .21 second and gradually increases until it averages .34 second at school age. In the adult the average for the R-T period is .36 second.

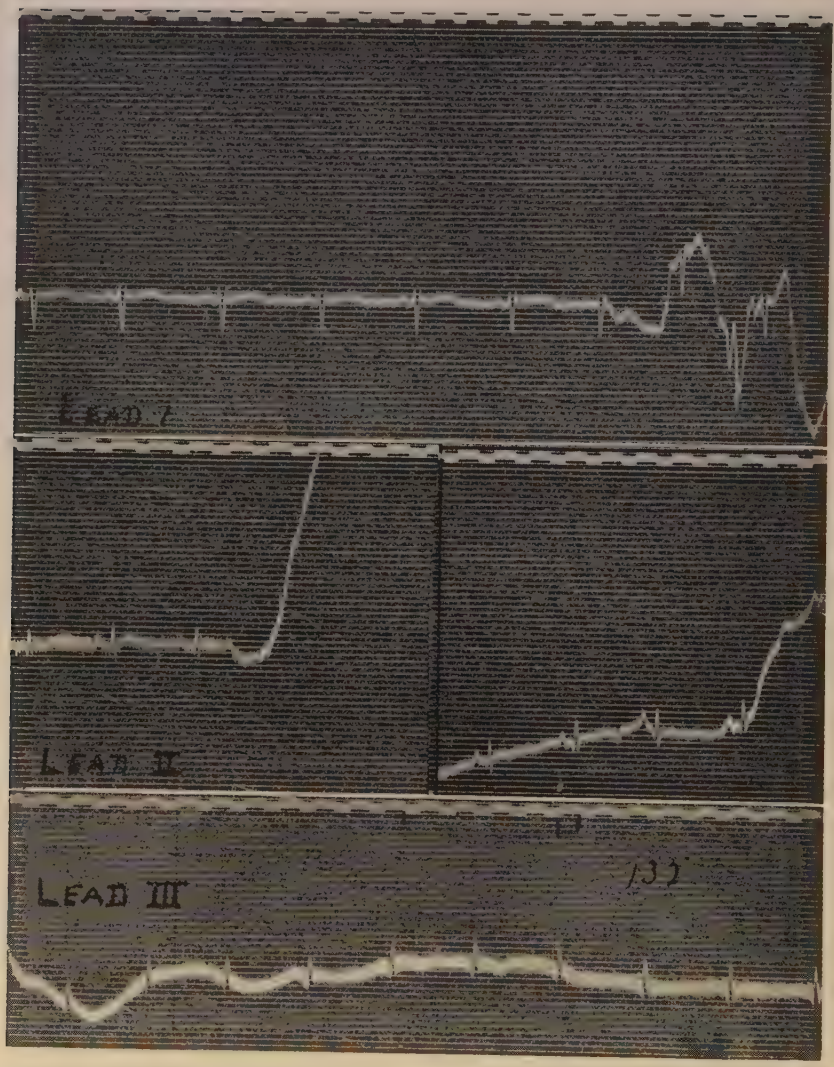

FIG. 92.—Electrocardiogram of normal newborn 48 hours old.

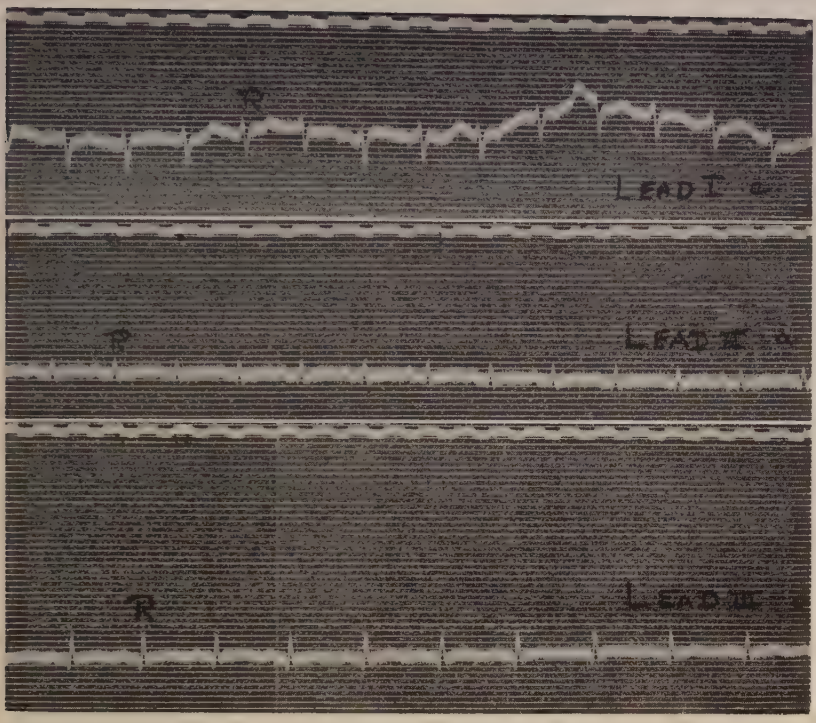

FIG. 93.—Electrocardiogram of newborn five days old.

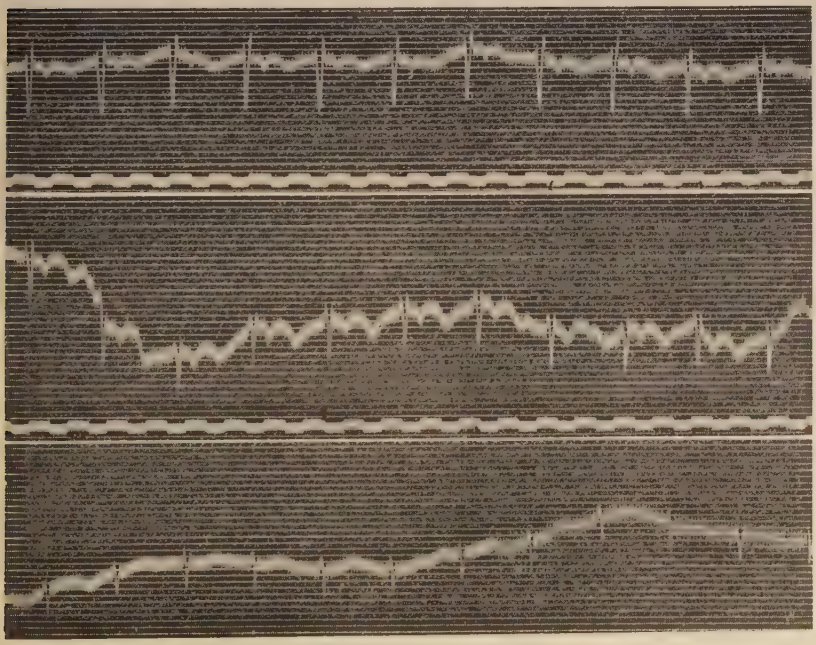

FIG. 94.—Electrocardiogram of the same newborn (Fig. 90) four weeks old.

12. The right ventricular preponderance which characterizes the first few months of life can be best explained by the relationship of muscle mass of the right and left ventricles.

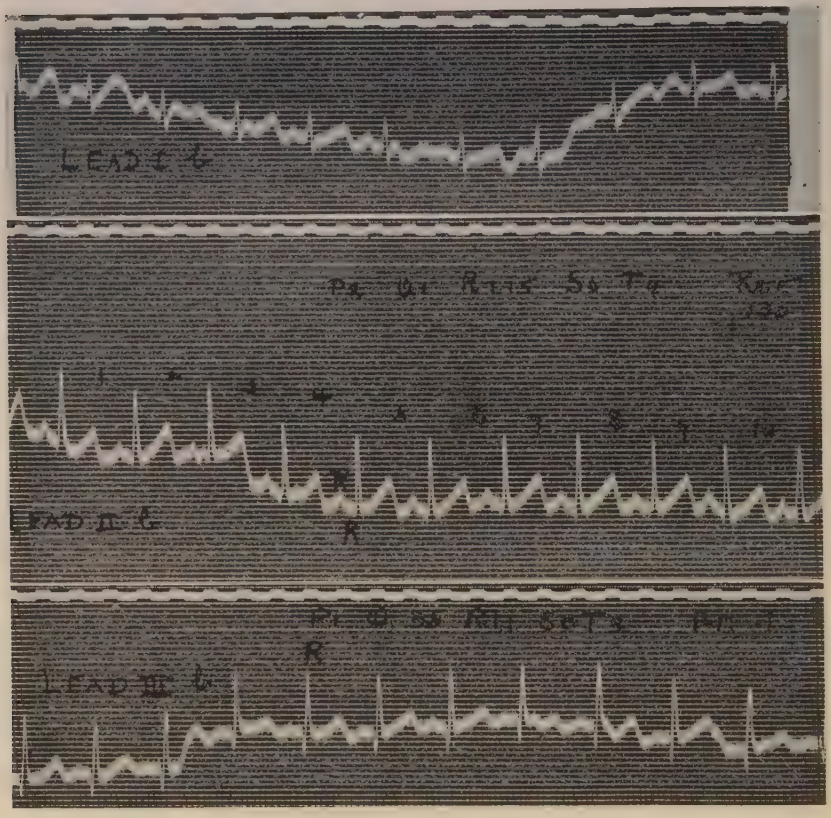

Fig. 95.—Electrocardiogram of the same newborn (Fig. 93) six months old.

THE ELECTROCARDIOGRAPH AS AN AID IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE

The differential diagnosis of congenital heart lesions, by means of physical examination and the Roentgen-ray apparatus is still inadequate and unsatisfactory. Considering the underlying pathology of congenital heart malformations and the fact that they are most commonly mixed lesions, considering further that the heart in an attempt to adjust itself to the required work of the body, changes the relationship in weight and capacity of the chambers, thereby changing the symptoms, one can readily see why the anatomical differentiation by clinical methods of diagnosis is uncertain and unreliable.

The electrocardiograph is the most accurate and precise means of modern medicine for determining the relationship between the chambers of the heart.

I made this electrocardiographic investigation in order to determine:

1. Whether there is a characteristic electrocardiogram in all congenital heart malformations as has been claimed by previous authors.

2. Whether the electrocardiographic diagnosis confirms the clinical and *x*-ray diagnoses.

3. Whether there is a definite and uniform relationship between the right and left side of the heart in these conditions.

4. Whether the conduction time shows a uniform abnormality.

Discussion of Earlier Studies.—The first electrocardiographic studies of congenital hearts were made by Steriopulo.[1] He investigated two cases of patent ductus arteriosus.

Case 1.—"Woman was 46 years old. The heart enlarged to the left, 5 to 9 cm. In the first space, there was heard a very strong systolic murmur."

The electrocardiogram, Lead I only showed:

Rate 75

P	0.25	P-R Interval	0.24 sec.
Q	0.2	R-T Interval	0.28 sec.
R	0.0		
S	0.4		
T	0.45		

Case 2.—"Man 21 years old, had heart trouble since childhood. Hypertrophy to the left; but especially enlarged to the right. A systolic and presystolic murmur is heard over the whole thorax."

Pulse rate 80

The electrocardiogram showed:

P	0.25	P-R Interval	0.14 sec.
Q	0.27	R-T Interval	0.28 sec.
R	0.0		
S	2.6		
T	1.2		

The histories and physical findings of the above cases are incomplete, and only Lead I was taken. No conclusions as to the value of the electrocardiogram can be drawn from the above investigation.

In 1912 Ratner[2] studied 17 cases of congenital hearts with special reference to the electrocardiogram. He writes, "We believe to be able to claim with surety that all congenital hearts are characterized by an extremely long S-wave. The electrocardiograms are extremely characteristic and therefore can and must be taken in consideration in diagnosis in doubtful cases."

After a careful review of Ratner's original dissertation, I do not believe that the above conclusions are justified. In the first place, he took only Lead I, which is insufficient; secondly, he did not record any of his electrocardiograms, nor did he give any measurements;

thirdly, he mentioned only the S-wave and omitted the rest of the complex. In Case 2, a child one day old, he did not take into consideration that a deep S_1 is a characteristic feature of a normal heart of a newborn. In Case 10, he does not mention the S-wave at all.

In 1913, Russoff[3] found a different type of curve in each of four cases of congenital pulmonary stenosis. He draws no conclusions.

In 1913, Hecht[4] investigated nine cases of congenital heart lesions with the electrocardiograph. In only two cases are the clinical diagnoses given. He also took only the first lead. One case was in a newborn, and therefore cannot be considered. In two cases the S-wave was lacking entirely. In all the other cases the S-curve was rather distinct. He draws no definite conclusions.

Lewis[5] has found exaggerated amplitudes in several congenital cases of pulmonary stenosis, but he never published his results.

McCullough in 1916[6] studied a series of 12 cases. He concludes "Congenital malformations of the heart do not produce a distinctive electrocardiogram but the type of curve will depend upon the secondary effect of the heart chambers. This effect is chiefly on the right side of the heart and malformations associated with a secondary relative right ventricular hypertrophy produce electrocardiograms with deep S-waves in Lead I and high R-waves in Lead III. Malformations not producing right ventricular hypertrophy fail to cause a characteristic change in the electrocardiogram."

In the present investigation 16 cases of congenital heart malformations have been studied clinically and electrocardiographically for a period of about 20 months. Some of these cases have been observed clinically for a longer period.

In all cases three leads have been recorded. At least two electrocardiograms were taken in each subject, in some four and five. Where more than two have been taken on one patient, the algebraic average has been recorded.

Small tightly fitting copper cuffs were used in the group of infants, in the older children the electrodes for adults were used. All tracings were taken with the subject lying on his back.

Case 1.—This baby was first seen when six months old. It was blue at birth. It weighed 6835 gm. It was dyspneic, the fingers were slightly clubbed, it had convulsive attacks since four months of age, during which attacks it became limp, cyanotic and frequently unconscious.

Physical Examination.—The child is poorly nourished, the nails, lips and tongue are blue. The precordium is enlarged. There is a marked pulsation all over the precordium, especially over the second, third and fourth interspaces. A murmur is heard throughout the entire cycle and is transmitted all over the chest and back. The pulmonary second sound is markedly accentuated. A systolic thrill is definitely felt over the base of the heart. Gerhardt's sign is present. The heart measures by percussion 3 to 6 cm.; the upper border is at the second rib. By the *X*-ray the heart is 8½ cm. long from the

large vessels to the apex, the width at the base of the heart is 3 cm.; the widest dimensions transversely are 9½ cm. The right border is 3 cm. and the left border 7 cm. from the midsternal line.

Clinical Diagnosis.—Pulmonary stenosis and patent ductus arteriosus; post-mortem diagnosis: Pulmonary stenosis, hypertrophy of right ventricle. Patent ductus arteriosus.

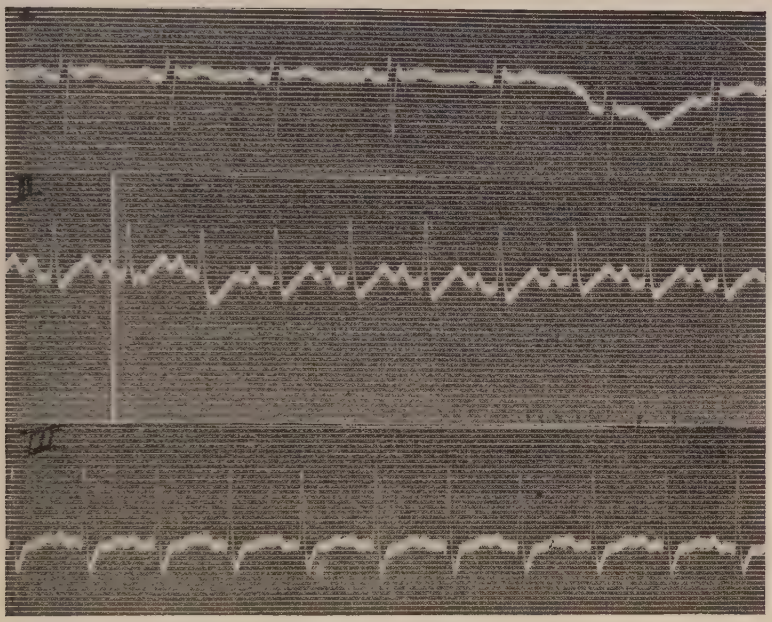

Fig. 96.—Case 1.

The electrocardiogram, taken on March 9, 1919 showed:

Rate 161—The P-R Interval is 0.14 sec. The P in Lead I is broad and diphasic in Lead III.

		Mvlt.		
Ld. I	R	0.3	Q-T Interval	0.25 sec.
	S	1.1	Q-S Interval	0.05 sec.
			S-T Interval	0.20 sec.
Ld. II	R	1.4		
	S	0.3		
Ld. III	R	1.5		
	S	0.3		

In this case the clinical diagnosis was confirmed by autopsy. The electrocardiograms showed a deep S_1 and high R_3, a rather characteristic meeting of the spikes of Lead I and Lead III which justifies an electrocardiographic diagnosis of right ventricular preponderance.

Case 2.—This boy is four years old, weighs 30 lb. and was first seen by us on May 6, 1919. He was not a blue baby. He was perfectly well the first year of his life. When he was two years old the mother was told by her family physician that the baby had heart trouble. During the last two years he has had quite frequent attacks of dyspnea upon the slightest exertion. He has always been underweight and very susceptible to "colds." There were no other symptoms of heart disease. P.E. The apex beat is diffuse and heaving. It can be seen and felt in the third, fourth and fifth interspaces. No thrill. The murmur is heard all over the chest and back, of the same intensity throughout the entire cycle replac-

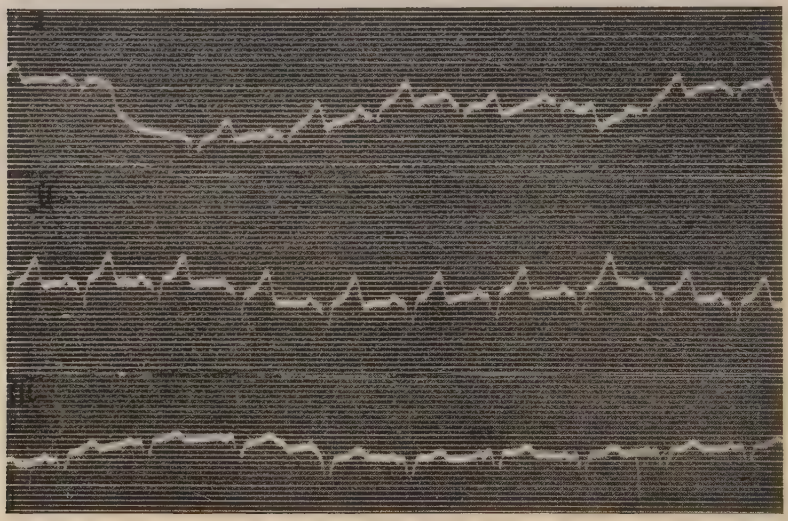

FIG. 97.—Case 2.

ing both sounds. It is humming top in character. The pulmonary second sound is quite accentuated. By percussion the heart measures 2 by 7 cm. Gerhardt's sign is absent. The *X*-ray shows a heart shadow of 14 cm. from the base to the apex, 11¼ cm. across the greatest transverse diameter, 3½ cm. from the middle of the sternum to the right border, and 8¼ cm. to the left border.

Clinical Diagnosis.—Patent ductus arteriosus. Five electrocardiograms were taken at intervals of seven days. Rate = 71. Sinus arrhythmia. Auricular extrasystole.

		Mvlt.		
Ld. I	R	0.9	P-R Interval	0.11 sec.
	S	0.1	R-T Interval	0.34 sec.
			Q-S Interval	0.04 sec.
Ld. II	R	1.5	S-T Interval	0.30 sec.
	S	0.4		
Ld. III	R	1.0		
	S	0.3		

The symptoms and physical examination point to a patent ductus arteriosus. The *X*-ray shows hypertrophy of both sides of the heart, but this is not confirmed by the electrocardiogram. The electrocardiogram shows a rather prominent T_1, an inverted P_3 and a deep Q in Leads II and III. There is no deep S in Lead I nor any exaggerated amplitudes which have been mentioned as characteristic of congenital heart lesions.

Case 3.—This girl, a sister of Case 2, was born a blue baby. When first seen she was six years old. She cannot lie flat on her back,

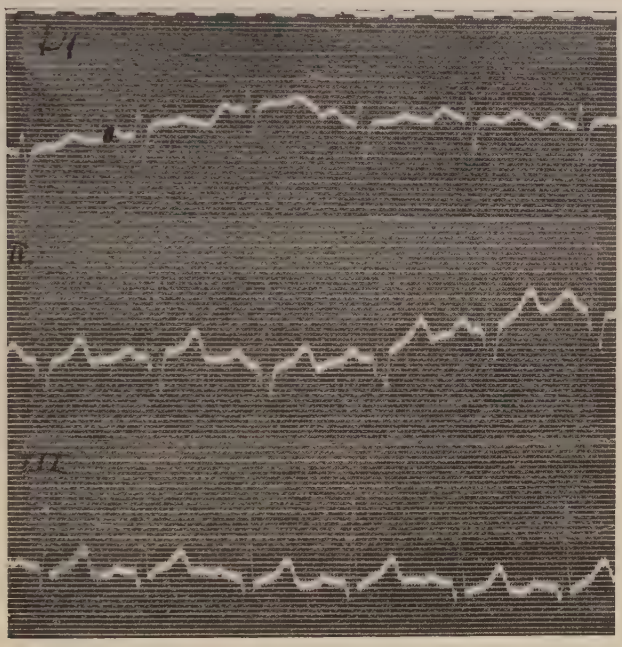

FIG. 98.—Case 3.

she needs at least two pillows. She becomes blue and dyspneic upon the slightest exertion. Physical Examination. The cheeks are dusky. The fingers are clubbed and watch-crystal in shape. The precordium is bulging. There is marked heaving of the entire chest. A definite systolic thrill is felt over the base of the heart. A systolic murmur is heard best at the pulmonary second interspace, transmitted over the entire chest and back. The heart beat is irregular, the arrhythmia being a sinus arrhythmia. By percussion the heart measures 3½ cm. to the right of the mid-sternal line and 7 cm. to the left. The upper border is at the third rib. The *X*-ray shows a total length of 13 cm., a width at the second space of 6½ cm.; a total width of 13 cm., and right and left borders respectively 4½ and 9 cm. from the mid-sternal line.

Clinical Diagnosis.—Pulmonary stenosis and patent ventricular septum. Electrocardiograms show: Rate = 106. Sinus arrhythmia.

P-R interval = 0.18 sec. Marked arching of curves. In Lead I the S is deeper than the R and in Leads II and III the Q and R are rather prominent. This is rather characteristic of a right ventricular hypertrophy and has been also considered by some authorities as characteristic of a congenital heart lesion. On account of the history and the presence of a systolic murmur the diagnosis of pulmonary stenosis is most likely, but the accentuated pulmonary second sound and a left-sided enlargement point to the possibility of another lesion, a patent auricular or ventricular septum. The above tracings confirm the clinical and *X*-ray diagnoses of an abnormal heart condition with hypertrophy, especially of the right heart.

		Mvlt.		
Ld. I	R	1.8	P-R Interval	0.18 sec.
	S	0.8	Q-S Interval	0.04 sec.
			S-T Interval	0.30 sec.
Ld. II	R	1.9		
	S	0.9		
Ld. III	R	0.6		
	S	0.2		

Case 4.—A boy of three years of age; weight 27 lb. His birth was normal. He has never been blue nor dyspneic. The mother

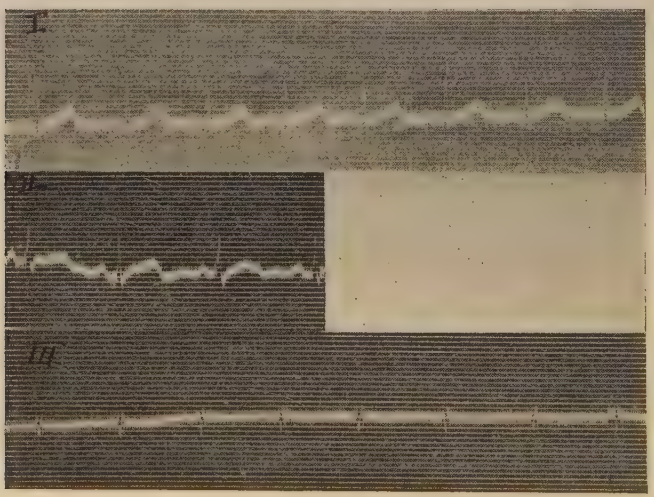

Fig. 99.—Case 4.

brought the child to us for circumcision not knowing that heart disease existed. He had a marked hypospadias, webbed toes and a depression over the coccyx. There was a loud systolic murmur heard best at the pulmonary second space and slightly to the left of the sternum. He has never had any of the common signs of heart disease. The heart was 1½ by 6 cm. by percussion. The *X*-ray showed no enlargement.

Rate 103. Sinus arrhythmia. This is a normal electrocardiogram.

		Mvlt.		
Ld. I	R	0.09	P-R Interval	0.15 sec.
	S	0.0	Q-S Interval	0.03 sec.
Ld. II	R	0.7	S-T Interval	0.27 sec.
	S	0.1		
Ld. III	R	0.1		
	S	0.0		

The diagnosis in this case is a patent auricular or ventricular septum.

Case 5.—An infant two years of age was first seen when two weeks old. Nothing was observed at that time except that there was a loud systolic murmur all over the chest, most audible over the pulmonary

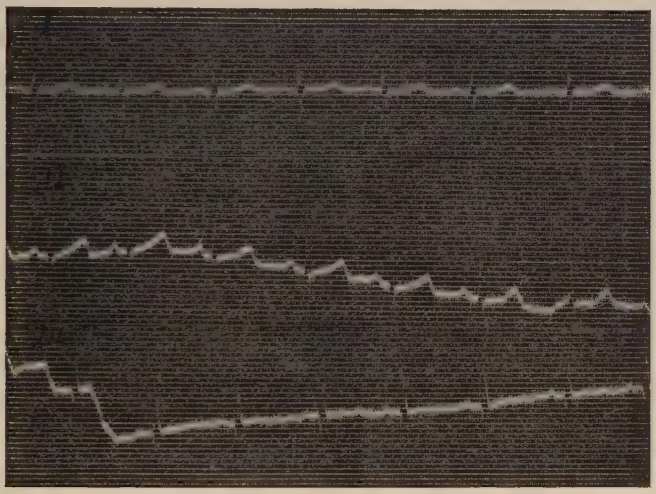

Fig. 100.—Case 5.

second space. At that time a diagnosis of patent foramen ovale or auricular septum was made. The murmur disappeared at about one year and since then there has been no sign of heart disease. The *X*-ray showed no enlargement. By percussion the heart measured 1½ by 5½ cm. Electrocardiograms were taken several times. Rate 110. There is evidence of a right ventricular hypertrophy shown in Lead I.

This case is probably a foramen ovale that remained open for about one year giving the constant murmur referred to above.

		Mvlt.		
Ld. I	R	0.2	P-R Interval	0.13 sec.
	S	0.3	Q-S Interval	0.20 sec.
Ld. II	R	0.6	S-T Interval	0.30 sec.
	S	0.1		
Ld. III	R	0.6		
	S	0.0		

Case 6.—This baby is a typical Mongolian idiot, age 15 months. The birth was normal, he was not blue. At the present time the weight of the baby is 6620 gm.; he is unable to sit up without assistance. There are no subjective signs of heart disease. P.E. By percussion the heart measures 1½ by 5 cm. A loud systolic murmur heard best at the pulmonary space is transmitted all over the chest. No *X*-ray was taken.

The electrocardiograms shows sinus arrhythmia. Rate 136. Marked arching of Lead II. There is practically no P in Leads I and III. Thickening of R_1 and R_2; S_2 is very deep. The deep S in Lead II is

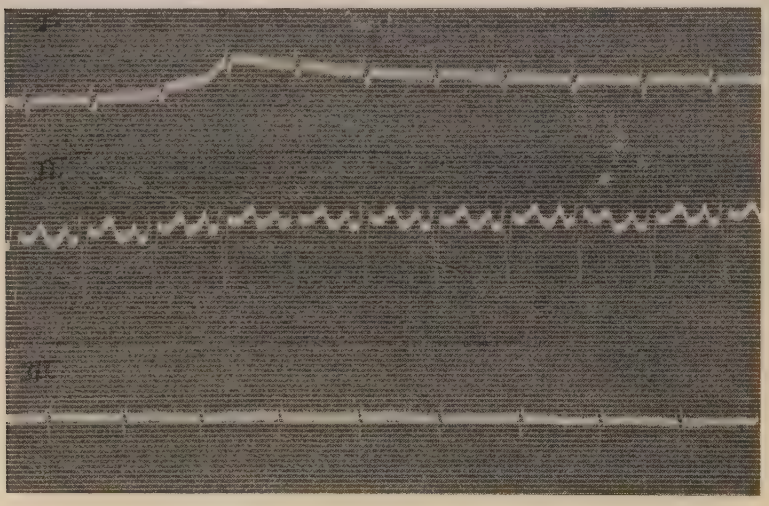

FIG. 101.—Case 6.

suggestive of a left ventricular hypertrophy. This case is most probably a patent auricular or ventricular septum with hypertrophy of the left ventricle.

		MVLT.
Ld. I	R	0.2
	S	0.2
Ld. II	R	0.3
	S	0.5
Ld. III	R	0.1
	S	0.3

P-O Interval	0.12 sec.
Q-S Interval	0.18 sec.
S-T Interval	0.20 sec.

Post-mortem Diagnosis.—The heart is greatly enlarged, the enlargement being principally on the right side. The heart weighs 120 gm. Its musculature is of a yellowish brown color speckled with numerous pinhead-size, opaque yellowish patches. The endocardium is also mottled with minute yellowish streaks giving the "tabby cat" appearance. There is a defect in the interventricular septum. The opening measures 2.3 cm. transversely and 1.6 cm. vertically. Through the posterior margin

of this foramen pass the posterior mitral and tricuspid leaflets which are joined to form one large strong leaflet. The left margin of this leaflet is attached by chordæ tendinæ to the papillary muscle of the left ventricle. The right margin is attached by chordæ tendinæ to the columnæ carnæ of the right ventricle. The anterior mitral and tricuspid leaflets are similarly fused to form a large leaflet with the margins attached by chordæ tendinæ to the papillary muscles of the left and right ventricles respectively. The aortic leaflets appear normal but the aortic ring is relatively small, measuring 3.5 cm. The pulmonary leaflets are normal and the ring measures 4.4 cm. The mitral ring measures 6.2 cm., the tricuspid ring 8 cm. The depth of the left ventricle is 5 cm. from the mitral to the apex and 6 cm. from the aortic leaflets to the apex. The depth of the right ventricle measures 4.5 cm. from the tricuspid to the apex and 5.5 cm. from the pulmonary valve to the apex. The left ventricular wall measures 7 mm. in thickness; the right 8 mm. The left pulmonary artery gives off two branches before it divides. The ductus arteriosus is closed. The foramen ovale is closed completely.

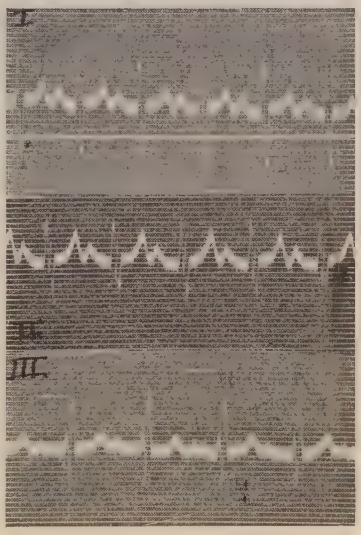

FIG. 102.—Case 7.

Case 7.—This baby was first seen at eight months of age. The birth was normal; the weight was 4950 gm. At one month the baby had an attack of dyspnea, drew up his legs and became cyanotic. He has been dyspneic ever since. The attacks continued on the average of about once every two weeks. He has not been gaining in weight, is very restless, sleeps only about an hour at a time, and is always distressed after feeding. The heart measures by percussion 2 by 6 cm. The *X*-ray shadow shows the right border to be 3 cm. from the midsternal line and the left border 6 cm. to the left. Electrocardiograms, taken four times, show a slight sinus arrhythmia.

			Mvlt.		
July 1. Ld.	I	R	0.8	P-R Interval	0.18 sec.
		S	1.0	Q-S Interval	0.10 sec.
Ld.	II	R	0.7	S-T Interval	0.20 sec.
		S	0.55		
Ld.	III	R	0.3		
		S	0.6		

P is rather prominent; the P-R interval is delayed. In the last tracing there is a definite splitting of the S-wave in Leads II and III. According to G. Canby Robinson this indicates impaired interven-

tricular conduction. The curves show both a right and left ventricular preponderance.

Case 8.—This baby is eight months old, weighs 9200 gm. His birth was normal. He gained very slowly during the first six months. His respirations have always been fast, his heart has always "thumped." He is now gaining in weight and doing quite well. His heart measures 2½ by 6 cm. by percussion. There is a marked thrill over the base of the heart. A typical "humming-top" murmur

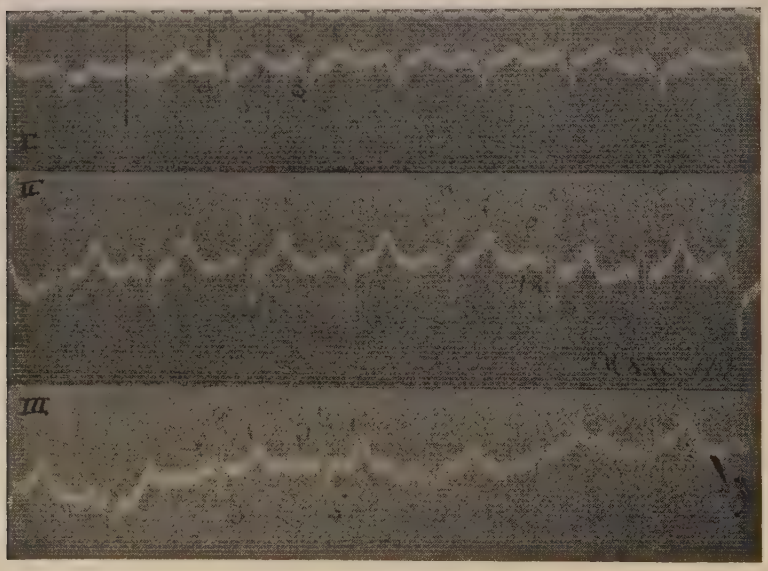

Fig. 103.—Case 8.

is heard all over the chest. The precordium bulges. The pulmonary second is markedly accentuated.

The electrocardiograms taken at intervals of one month show: Rate = 110. Rather high amplitudes and split R_3 and S_3 indicating an asynchronism of the ventricles and an impaired interventricular condition.

			Mvlt.		
Ld.	I	R	1.0	P-R Interval	0.12 sec.
		S	0.2	Q-S Interval	0.70 sec.
Ld.	II	R	1.0	S-T Interval	0.28 sec.
		S	0.6		
Ld.	III	R	0.5		
		S	0.6		

Clinically this is a typical case of patent ductus arteriosus and electrocardiographically it has the exaggerated amplitudes found in congenital hearts.

Case 9.—This boy is eight years old. His only complaint was weakness. The mother did not know that the child had heart trouble. The heart is normal in size both by percussion and the *X*-ray. There is a systolic murmur at the third interspace which is transmitted to the left and down the sternum, but no murmur is heard at the apex. There is no thrill. The pulmonary second sound is accentuated. In spite of the absence of an enlargement a diagnosis of patent auricular septum was made because of the nature of the murmur, its character

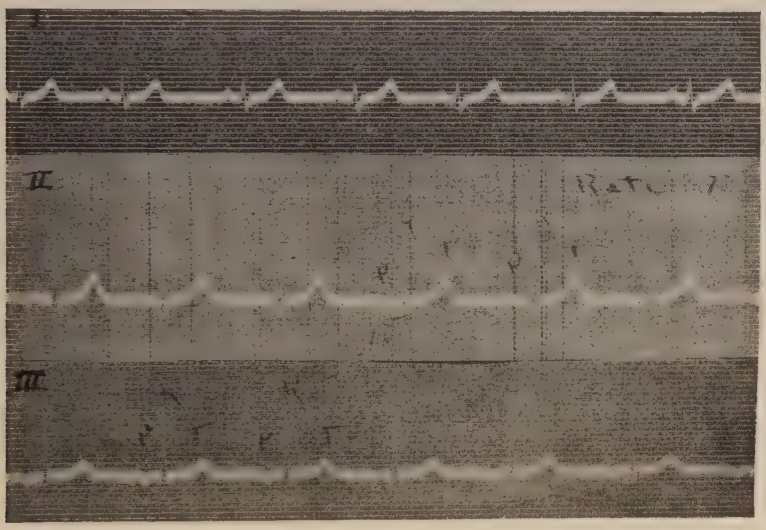

Fig. 104.—Case 9.

and transmission. Electrocardiograms were taken on several occasions and showed sinus arrhythmia. The T-waves are rather high. Rate = 96.

			Mvlt.		
Ld.	I	R	0.4	P-R Interval	0.13 sec.
		S	0.2	Q-S Interval	0.03 sec.
Ld.	II	R	1.2	S-T Interval	0.29 sec.
		S	0.1		
Ld.	III	R	0.2		
		S	0.0		

This is a normal tracing.

Case 10.—A child, age three years, weighing 28 lb., was brought to us with the complaint of nervousness. It had never had any of the usual signs of heart disease. The physical examination was negative except for a loud systolic murmur heard with the same intensity

throughout the entire cycle, at the third interspace and slightly to the left of the sternum. There was no thrill. The heart measured by percussion and also by *X*-ray 3 by 6 cm. Electrocardiograms showed slight sinus arrhythmia. Rate 105.

		Mvlt.		
Ld. I	R	0.6	Q-S Interval	0.03 sec.
	S	0.2	S-T Interval	0.25 sec.
Ld. II	R	1.4		
	S	0.3		
Ld. III (Was not obtained).				

This is a normal electrodiogram.

Case 11.—This patient is two and one-half years old. The clinical diagnosis is a patent auricular or ventricular septum. He was a blue baby at birth but has not been blue since. He has always been delicate and frail. He was brought in for examination because he was below weight and tired easily. P.E. Fairly well developed child. There is an internal strabismus of the right eye. The apex beat is diffuse, heaving and can be felt and seen in the second, third and fourth interspaces. There is no thrill. On the first examination the heart was 2 by 7 cm. by percussion, one month later it measured 2½ by 7 cm., and three months hence measured 2½ by 7 cm. A very loud systolic murmur is heard all over the chest, best heard over the mitral area. The pulmonary second sound is accentuated. The *X*-ray shows a globular heart with a mitral configuration. It is 5 cm. at the base, 9½ cm. transversely, the right border being 2½, the left 7 cm. from the mid-sternal line.

Electrocardiogram.

		Mvlt.		
Ld. I	R	0.6	P-R Interval	0.15 sec.
	S	0.3	Q-S Interval	0.07 sec.
Ld. II	R	0.3	S-T Interval	0.22 sec.
	S	0.5		
Ld. III	R	0.2		
	S	0.2		

Rate = 120. Slight sinus arrhythmia. There is rather a broad P in all three leads which is an indication of delayed conduction through the auricle. Lead I is suggestive of a right ventricular preponderance, and Lead III of an impaired interventricular conduction. T_3 is inverted. This is quite a common occurrence in normal infants. The electrocardiographic diagnosis of right ventricular hypertrophy confirms the clinical and *X*-ray diagnosis.

Case 12.—This patient is three and one-half years of age. Her birth was normal, she has never been blue. The mother was told a year ago that the child had heart trouble. Her chief complaint was poor appetite and failure to gain. Physical examination revealed many carious teeth and diseased tonsils. She was poorly developed

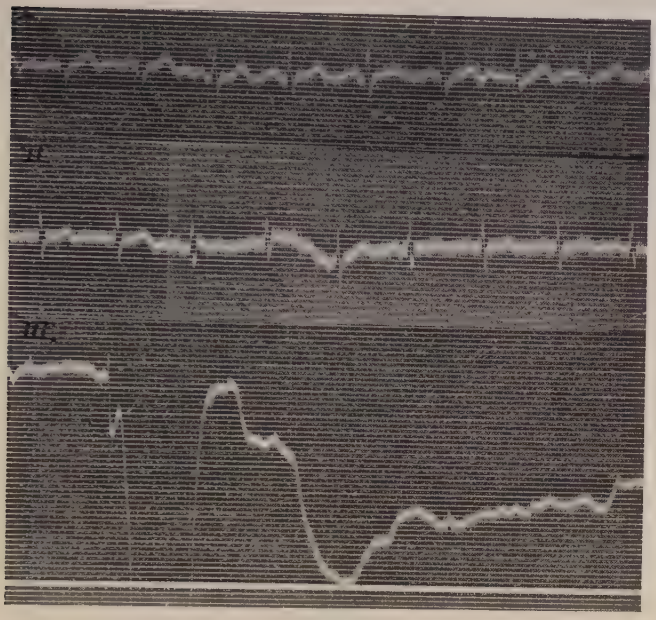

FIG. 105.—Case 10.

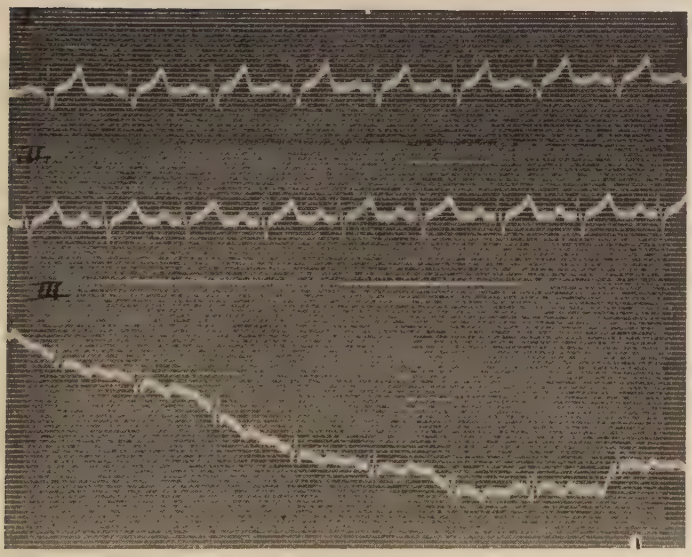

FIG. 106.—Case 11.

and nourished. The apex beat is diffuse and heaving, 1 cm. outside the nipple line. A systolic thrill is felt at the base. A loud systolic murmur is heard; it is localized at the third interspace and to the left of the sternum. The heart measures by percussion 2½ by 7 cm. No *X*-ray picture was taken.

Clinical Diagnosis.—Congenital heart defect. Patent septum, auricular or ventricular. Electrocardiograms: The rate is 115; sinus

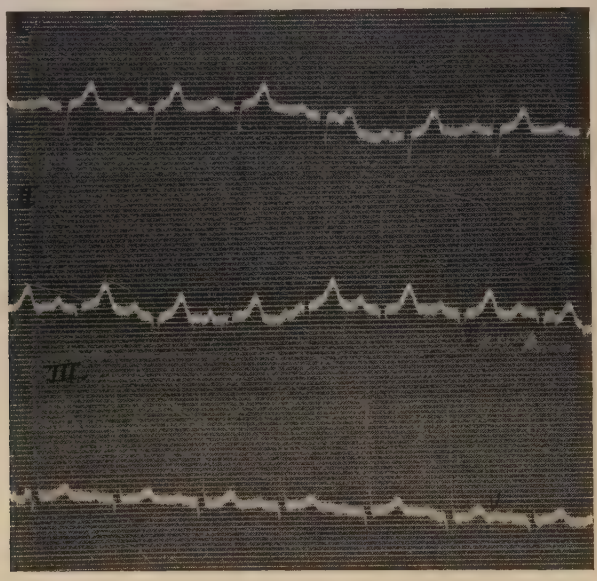

Fig. 107.—Case 12.

arrhythmia; P-R equals 0.18 second. The very high R_2 and R_3, the relatively deep S_1 are indicative of a right ventricular preponderance.

		Mvlt.		
Ld. I	R	0.5	P-R Interval	0.18 sec.
	S	0.6	Q-S Interval	0.03 sec.
Ld. II	R	1.9	S-T Interval	0.22 sec.
	S	0.1		
Ld. III	R	2.2		
	S	Nil		

The electrocardiograms confirm the clinical diagnosis of a congenital heart.

Case 13.—Clinical diagnosis: Pulmonary stenosis and patent septum, auricular or ventricular.

This patient was a colored girl, aged three and one-half years. She was born a blue-black baby. She has always been undernourished and subject to "colds." She coughs continuously and gets cyanotic upon crying or the slightest exertion. She is an underdeveloped and undernourished child. She has a very dusky bluish color over the

entire body surface. Her fingers and toes are markedly clubbed. Her heart is 3½ by 7 cm. by percussion. There is a definite systolic thrill felt over the base. The first sound at the apex is completely obliterated by a loud systolic murmur. This murmur is heard best at the left of the sternum at about the third interspace. It is transmitted slightly to the axilla and along the left of the sternum. The pulmonary second sound and the first sound at the lower end of the sternum are accentuated. *X*-ray diagnosis: Mitral heart (3 by 8 cm.) at the widest portion. Electrocardiograms were taken on November 7, 14

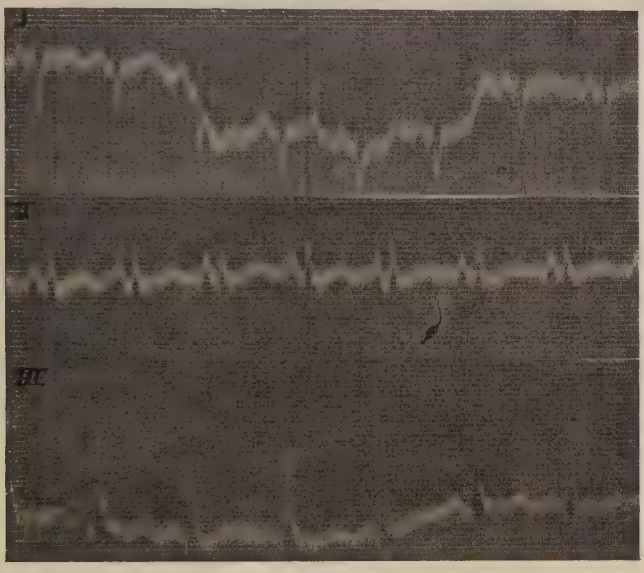

Fig. 108.—Case 13.

and 28, 1919. There is a definite right ventricular preponderance as can be seen in the following tabulation. By the use of White's formula (–24) is obtained. The heart rate is normal. The notching of the S_1 and R_2 is suggestive of a possible myocardial fatigue.

		Mvlt.		
Ld. I	R	0.3	Q-S Interval	0.05 sec.
	S	1.0	S-T Interval	0.22 sec.
Ld. II	R	0.6		
	S	0.2		
Ld. III	R	0.8		
	S	0.1		

The electrocardiograms confirm the clinical diagnosis.

Case 14.—This case is a girl baby aged 19 months. Her family history is negative. She was normal at birth and has never had any signs of heart disease. She was brought to the clinic

for a "running ear." She had a purulent discharge from the left ear. She is slightly undernourished. Except for the heart she shows nothing unusual. Her heart measures by percussion 2 by 6½ cm. The apex beat is in the fourth space 1 cm. outside of the nipple line. There is a systolic murmur heard best at the second interspace to the left of the sternum. The murmur is heard less distinctly at the apex and is not transmitted to the left. The pulmonary second sound is not accentuated. Clinical diagnosis: A patent septum, most

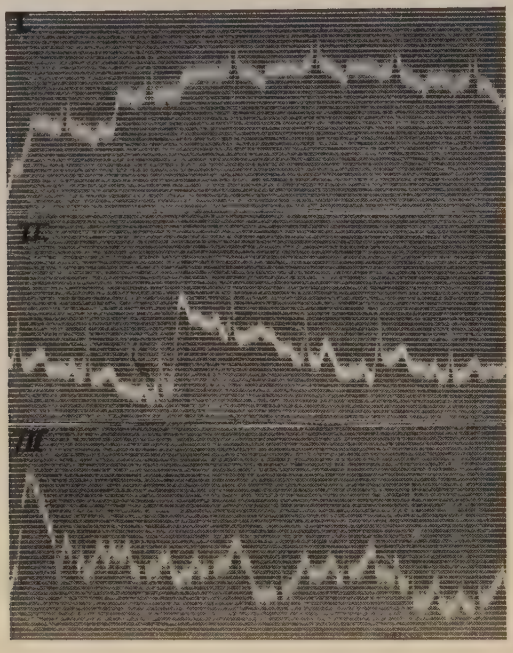

Fig. 109.—Case 14.

probably auricular. Electrocardiograms were taken December 1 and 23, 1919. They show a right ventricular preponderance.

		Mvlt.		
Ld. I	R	0.3	Q-S Interval	0.07 sec.
	S	0.7	S-T Interval	0.22 sec.
Ld. II	R	0.8		
	S	0.1		
Ld. III	R	1.7		
	S	0.2		

Case 15.—A girl four years of age. Her family history is negative. She was brought in for examination on account of "nervousness." She has no signs nor symptoms of heart disease. She is slightly undernourished, but otherwise presents no abnormal condition upon physical examination. Her heart is 2 by 6½ cm. by percussion,

and 2 by 7 cm. by the *X*-ray. A systolic murmur is heard only at the third interspace just at the left of the sternum. The pulmonary second sound is not accentuated. Electrocardiograms were taken on November 25, and December 4, 1919.

		Mvlt.		
Ld. I	R	0.2	Q-S Interval	0.03 sec.
	S	0.6	S-T Interval	0.25 sec.
Ld. II	R	0.7		
	S	0.3		
Ld. III	R	0.8		
	S	0.1		

A clinical diagnosis of patent auricular or ventricular septum was made because of the murmur and the age of the patient. The

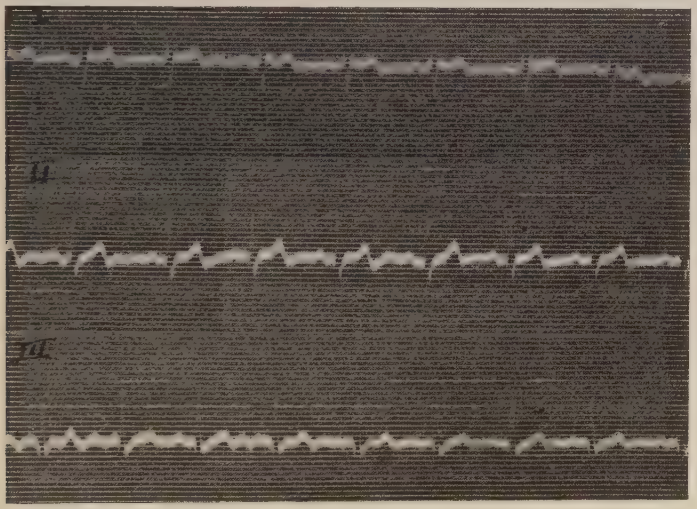

Fig. 110.—Case 15.

electrocardiographic diagnosis, right ventricular preponderance (–9), is not confirmed by any clinical signs, nor by the *X*-ray plates.

Case 16.—A girl baby, 21 months old. (Her sister, also a blue baby, died when two weeks old.) She has been blue since birth, very frail, started to walk at 20 months; the mental development is retarded. When the baby was one week old, the mother was told of the child's heart trouble. The child is markedly cyanotic and dyspneic; her fingers and toes are markedly clubbed. The respiration is 68 per minute; the precordium is bulging. The heart dulness extends 3½ cm. to the right and 7 cm. to the left of the mid-sternal line. Roentgen-ray examination showed the heart 4 cm. to the right and 7 cm. to the left of the mid-vertebral line. For a child 21 months old this is a marked enlargement to the left. The child was under observation for a period of

about six months and at no time could a murmur be heard. The heart sounds are always fast, regular and slapping in character. Both sounds, at the pulmonary area as well as over the tricuspid, are markedly accentuated. The liver and spleen are in their normal position and are easily palpable. There is considerable congestion in the bases of the lungs. The roentgenologist believed that a pouching and enlargement of the great vessels were present especially at the aortic arch to the right. His diagnosis was: Transposition of the great

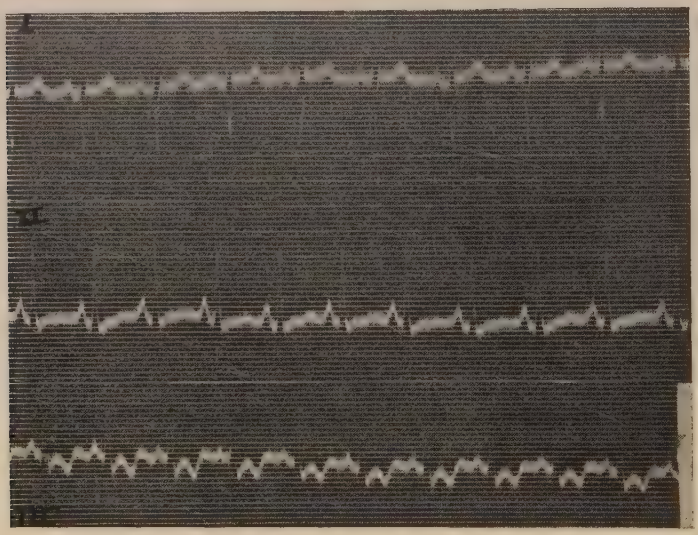

FIG. 111.—Case 16.

vessels. Electrocardiograms were taken over a long period, nine records in all. They all were remarkably similar.

		Mvlt.		
Ld. I	R	0.1	Q-S Interval	0.07 sec.
	S	1.2	S-T Interval	0.18 sec.
Ld. II	R	1.5		
	S	0.2		
Ld. III	R	3.0		
	S	0.2		

The R_2 is notched and the T_3 is inverted. The electrocardiograms show a right ventricular preponderance (–39) confirming both the clinical and *X*-ray diagnoses.

Discussion.—Since the electrocardiograms of normal infants show a physiologic right ventricular preponderance during the first three or four months of life, no cases under six months of age were studied.

The diagnosis (by means of the electrocardiogram) of right ventricular preponderance was only made from tracings with a deep S_1

and a high R_3 or for which White's formula $(U_1 + D_3) - (D_1 + U_3)$ was negative.

The clinical diagnosis in 4 of the 16 cases was pulmonary stenosis associated with some other lesion, in 2 cases patent ductus arteriosus, in 1 case patent foramen ovale which later on became closed. One case was believed to be a transposition of the great vessels. The other 8 cases were diagnosed patent septa, either auricular or ventricular.

The electrocardiographic diagnosis was right ventricular preponderance for 9 cases. These include 4 cases of pulmonary stenosis, one case of patent septum ovale, one case of transposition of the great vessels and 3 cases of patent septa either auricular or ventricular (Tables 18 and 19).

The electrocardiogram of:

Case 8 (clinical diagnosis: Patent ductus arteriosus) and Case 16 (clinical diagnosis: Transposition of the great vessels) exhibited exaggerated amplitudes, which, according to Lewis, are diagnostic of congenital heart disease.

Case 6 (clinical diagnosis: Patent interventricular septum) and Case 8 (clinical diagnosis: Patent ductus arteriosus) were diagnosed electrocardiographically left ventricular preponderance, which was not confirmed by the clinical or *X*-ray diagnosis.

In only five of the nine cases of right ventricular preponderance did the electrocardiographic diagnosis agree with the clinical diagnosis (Cases 1, 3, 7, 13, and 16).

Of the two cases of patent ductus arteriosus (Cases 2 and 8) one showed a normal electrocardiogram (Case 2), the other a combination of left ventricular preponderance and exaggerated amplitudes. Of the seven cases that were diagnosed clinically patent interventricular or interauricular septum, only three cases (Cases 12, 14 and 15) showed a right ventricular preponderance.

In Case 5 (foramen ovale) a murmur was heard only up to the seventh month. The electrocardiographic diagnosis of a right ventricular preponderance could not be confirmed clinically.

The conduction time in the above tracings is hardly of any value in diagnosis. The average normal conduction time during the various periods of childhood is as follows:

	P-Q	Q-S	S-T
Under 1 year	0.113	0.036	0.211
From 1 to 5 years	0.125	0.049	0.213
From 6 to 12 years	0.138	0.069	0.273

The P-Q Interval in the cases under discussion under one year ranges from 0.12 to 0.18 second. The Q-S and the S-T intervals for this period are also lengthened (respectively 0.05 and 0.22 second).

In the next period from one to five years, the average of the P-Q interval is 0.13 second. This is an insignificant increase over the normal. The Q-S and the S-T periods are respectively 0.055 and

0.22 second. In 55 per cent. of the cases the S-T was 0.25 second or over. In the last period, 6 to 13 years, the average for the P-Q, Q-S and S-T intervals was 0.15, 0.055 and 0.275 second respectively. In this period the combined Q-T is over 0.30 second in all cases.

Conclusions.—1. The electrocardiograms of congenital heart lesions are not always characteristic.

2. The electrocardiograms of congenital heart lesions are not always abnormal.

3. Nine cases out of sixteen with a clinical diagnosis of congenital heart gave electrocardiograms showing right ventricular preponderance.

4. In only five of these nine cases did the clinical diagnosis confirm the diagnosis of the electrocardiograph.

5. Two cases exhibited "exaggerated amplitudes."

6. The P-Q interval was slightly prolonged in almost all instances. This increase however, is so slight that its value for diagnosis is doubtful.

7. The Q-T interval is uniformly prolonged for all ages in almost all tracings. This increase may be of value as an aid in the diagnosis of congenital heart disease.

8. The split R and S is found quite frequently in the electrocardiogram of congenital heart disease.

Arrhythmias.—The subject of arrhythmias in childhood needs revision and reclassification. Although the electrocardiograph and the polygraph have helped to establish a scientific basis for the classification of arrhythmias in the adult no such study has as yet been carried out for childhood.

Investigations with special reference to the peculiarities of childhood are necessary to determine the different forms of irregularity, their frequency, their cause and mode of production.

Cardiac irregularities are much more common in children than in adults. On account of the weak inhibitory mechanism and the instability of the circulatory system, the pulse is easily susceptible to irregularities. Arrhythmias occur very frequently in nervous children. They may occur in typhoid fever and other acute infections, in alimentary intoxication, in any digestive disturbances, in anemia. Mackenzie has made the statement that in all children he examined the pulse was irregular at one time or another.

Although some of the irregularities can be differentiated clinically, the electrocardiogram is necessary to differentiate the benign from the serious types and to determine the exact source of all ectopic impulses.

Sinus Arrhythmia.—This type of arrhythmia is known as youthful or vagal arrhythmia because it occurs most frequently in the youthful person and is dependent upon vagus stimulation. The cardio-respiratory centers in children are more susceptible to external influences than in the adult. Rhythm and rate are more unstable. Mackenzie called this type of irregularity sinus arrhythmia, because the impulse

for each beat arises in the sinus region of the heart. This condition can usually be diagnosed clinically. At times it manifests itself by skipping of a beat, at other times it is irregular in rate and strength. Fig. 112 shows the constant relationship between the two phases of respiration and this form of arrhythmia. Apnea stops the arrhythmia. The faster the pulse the less the degree of arrhythmia and the slower the pulse the greater the irregularity. Atropin, by paralyzing the ends of the vagus, causes an increase of the pulse rate and eliminates the arrhythmia.

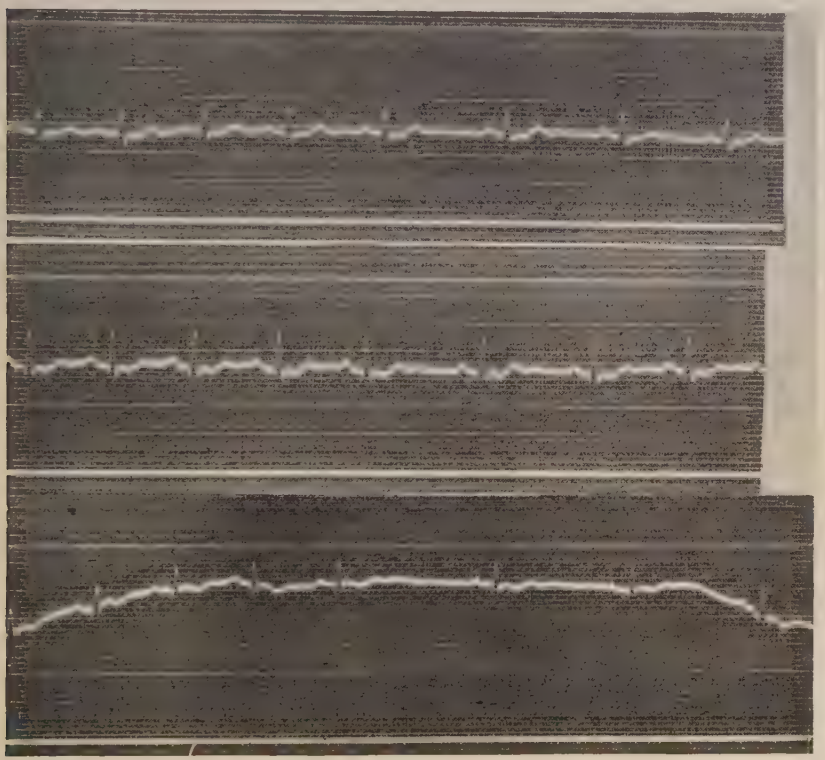

FIG. 112.—Sinus arrhythmia, respiratory T-P varies from 0.16 second to 00.42 second.

Table 20 (Friberger's, Hecht's and author's) shows the percentage of sinus arrhythmia in the different ages.

The electrocardiogram in a sinus arrhythmia shows a normal tracing as to size and form of all the complexes; the diastole is lengthened and there may be a very slight variation in the height of the P-, R- and T-waves.

Electrocardiographically, a sinus arrhythmia is considered to be present if there is a difference of one-tenth second or more between the shortest and longest pulse periods in the same tracing (Fig. 112).

Extra-systoles.—An extra-systole is a premature contraction of the heart which arises from some other region than the sino-auricular node.

In the majority of cases it is easily recognizable by auscultation of the heart or by palpation of the pulse, but it is impossible to determine the exact origin of this abnormal impulse except with the electrocardiograph. If the origin is in the auricle it is known as an auricular extra-systole, if in the ventricle a ventricular. In an auricular extrasystole the P-wave either disappears or has an abnormal shape and position, whereas the ventricle remains intact; the opposite is true in the ventricular type.

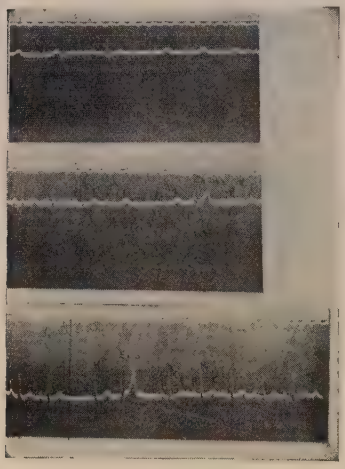

Fig. 113.

There is a difference of opinion as to the frequency of extra-systole and its relation to cardiac disease. Lewis found it only rarely before the end of the first decade of life; associated with an infectious disease. It seems to be the concensus that in children premature contractions arising in the auricles are more common than those arising elsewhere. The opposite of this is true in adults. Gunson in a polygraphic investigation found auricular extra-systoles in 28 per cent. of diphtheria cases while no ventricular extra-systoles were observed. The premature beats were isolated in all but five cases and accompanied

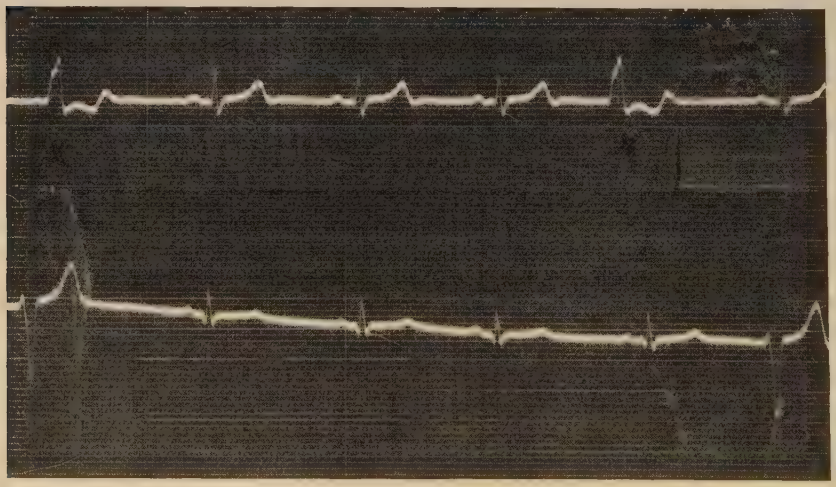

Fig. 114.—Extrasystoles, left ventricular, with compensatory pause. Boy ten years old. Functional arrhythmia. No heart disease.

by signs of cardiac dissociation with gallop rhythm. Ventricular extrasystoles have been reported in children by Gunson, Lewis and Allen and Hume. Visco observed premature contractions 48 times in a series of 1000 children, twice in normal children, 18 times in digestive distur-

bances and infections, once after the taking of belladonna, 14 times in dyscrasias, 3 times in epilepsy and 10 times in convalescent patients. He considered them of very little significance. Hecht and others, however, do not agree with him.

Hecht believes that auricular extra-systoles are quite common in children. The prognosis is said to be better in the auricular than in the ventricular type. In three cases the writer has observed, two were in apparently normal children, and the third was in a myocarditis following influenza. There were no subjective symptoms in the first two children, but the third child (S. H.), Fig. 113, complained of palpitation of the heart and was quite weak for several

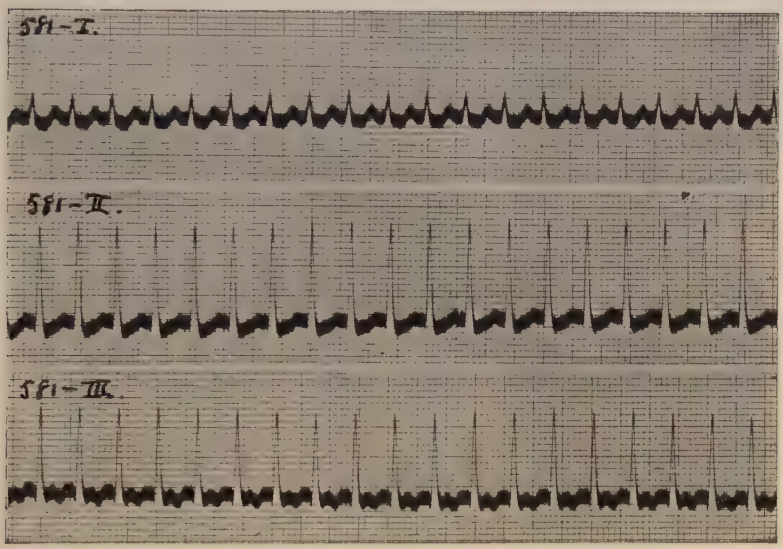

FIG. 115.—Electrocardiogram during the period of tachycardia. (Strong, in "Medical Clinics of North America," January, 1919.)

months following the attack of influenza. She was electrocardiographed many times during the course of the next six months and extra-systoles always appeared as shown in the curve.

Paroxysmal Tachycardia.—Paroxysmal tachycardia is characterized by a very rapid heart rate, usually over 180 beats per minute, in which the center of impulse formation has changed from the normal location to some other part of the auricle. The ventricular beat is usually regular although very rapid. In paroxysmal tachycardia the pulse is somewhat slower than in auricular flutter. In the former, the ventricular rate is equal to the auricular, whereas in the latter there may be a heart-block with the auricle beating two or three times as fast as the ventricle. Paroxysmal tachycardia is rare in childhood, only 17 cases being recorded in the literature. Table 21 shows each case in detail. The first 10 cases were taken verbatim

from Brown the other 7 have been obtained from miscellaneous sources described in Table 18.

The cases occurred in children at the ages of from 3 months to 13 years. Among the predisposing factors are mentioned measles (3 cases), scarlet fever, diphtheria, gastro-intestinal disorders, chickenpox (?).

The time of the onset varied from three months to six years; the attacks recurred in the majority of cases on the third, fourth or fifth day. The individual attacks lasted from a few minutes to 12 days. There was an increase in the pulse rate from the normal to from 180 to 300 beats. The normal pulse rates in these children ranged between 64 to 112. About half of the cases were in no special distress even at the

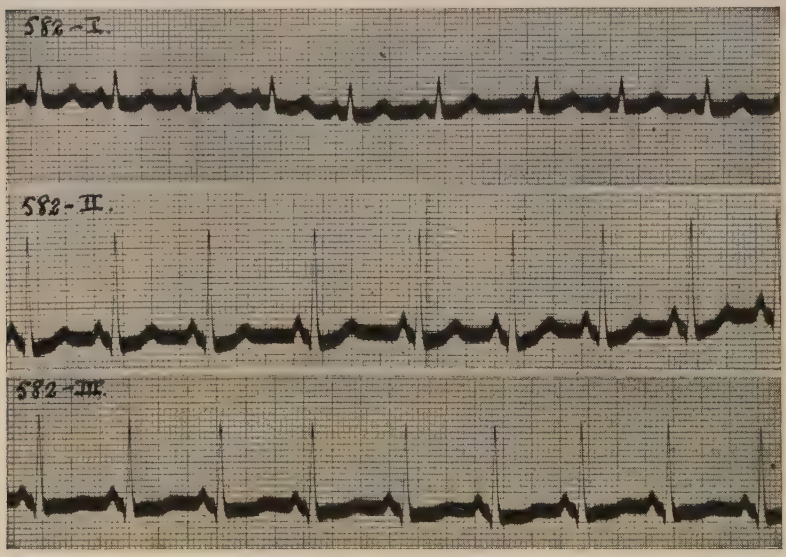

FIG. 116.—Electrocardiogram after the resumption of the normal sinus rhythm. (Strong in "Medical Clinics of North America," January, 1919.)

height of the paroxysm but in the other half there were many severe symptoms of cardiac decompensation. Pallor, dizziness, dyspnea, in several instances orthopnea, cyanosis, cardiac dilatation, hemoptysis, vomiting, general edema, and collapse were present. Of the cases reported two died during an attack, in six the progress was not reported, seven probably recovered (the period of observation not being known), and one is reported as having improved. Electrocardiograms were taken in only nine of the cases reported.

Heart-block.—A heart-block may be defined as an abnormal heart mechanism in which there is a delay in or an absence of a response by the ventricle of the auricular impulse. The first authentic heart-block reported was that of V. Starck in 1903, but he did not take any records. (The diagnosis of heart-block in childhood could not be graphically established before 1910.)

Another case, observed by the author is included in Table 15. Thirty-one cases of heart-block in children are reported in the literature, as far as the author is aware. Seventeen are complete heart-blocks, five partial and the remaining unspecified. The ages of these children range from 15 months to 15 years. Fourteen of the children showed a continuous, six a recurrent heart-block. The dissociation lasted from 3 days to 11 years; in the majority of cases, however, the duration of

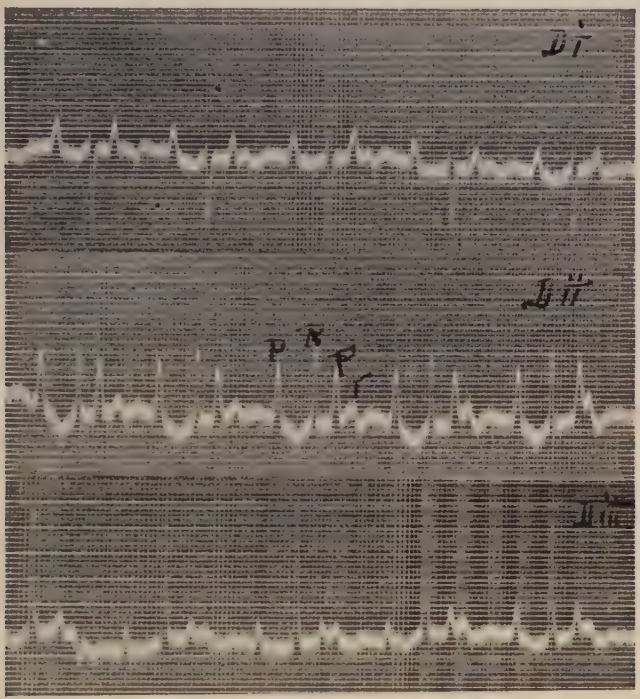

FIG. 117.—Rate ventricular—65. Rate auricular—130. PR—.28 sec. P_1 is exaggerated and P_2 most marked. Inverted T_1. Marked right preponderance 2:1 Heart-block. Diagnosis—congenital pulmonary stenosis and 2:1 heart-block—Case 32, Table 15—Girl, age nine—born blue baby. Has always been cyanotic; cyanosis and dyspnea have been getting worse, girl has been going to school for two years, walking to and from school. Had measles when six years without any complications. Had severe attack of influenza when seven years and pertussis when four years. Has been having rheumatism of all the muscles (growing pains last two years). *P.E.* Marked cyanosis of all mucous membranes. Clubbing of fingers and toes, dyspnea while at rest, tonsils enlarged and diseased, jugular pulsation visible, marked thrill over base of the heart, definite systolic murmur heard all over the precordium. Transmitted to the left into the axilla and also up into the vessels of the neck. Jugular pulse 100 to 110 and radial 50 to 55 per minute. Hg 90 per cent. R.b.c. = 5 to 7 million. Hg index 150 to 160 per cent. Girl is going to school daily, and is able to walk slowly.

the heart-block was less than one year. Nine of the cases were associated with congenital heart lesions, nine with diphtheria, two with rheumatism, one with a cardiac tumor, one with influenza, one with congenital lues, one with measles, and one was due to some pyogenic

organism. Ten of the cases ended fatally, three were reported to have recovered and the others are not accounted for. The Stokes-Adams syndrome occurred in 14 of the cases and was absent in 8. The electrocardiograph or the polygraph or both were used in 16 cases (Table 15.)

TABLE 15.—REVIEW OF 32 CASES OF HEART-BLOCK IN CHILDREN

Case	Date	Author	Reference	Age	Sex
1	1896	Schuster	Deutsch med. Wchnschr. 22: 484.	4 yr.	M
2	1901	Marquio	Arch. de med. d. enf., 4, 467.	8 yr.	M
3	1901	Marquio	.....	5 yr.	M
4	1903	v. Stark	Monatschr. f. Kinderh., 2: 11.	5 yr.	M
5	1908	Dunn	J. A. M. A., 50: 1985.	11 yr.	M
6	1908	v. d. Heuvel	Proefschr. v. Groeningen.	13 yr.	F
7	1910	Fulton, Judson and Norris	Am. J. M. Sc., 140: 339.	2 yr.	M
8	1910	Magnus, Alsleben	Ztschr. f. klin. Med., 69: 82.	8 yr.	M
9	1910	Fleming and Kennedy	Heart, 2: 77.	10 yr.	F
10	1911	Price and Mackenzie	Heart, 3: 233.	9 yr.	F
11	1911	Heilhecker	Ztschr. f. Path., 8: 319.	14 yr.	M
12	1911	Armstrong and Moncke	Deutsch. Arch. f. klin. Med., 102: 14.	5 yr.	M
13	1914	Hecht	Wien. med. Wchnschr., 64: 178.	9 yr.	M
14	1914	Hecht	.....	3 yr.	M
15	1915	d'Espine	Bull. de l'Acad. de. med., 74: 292.	8 yr.	M
16	1915	Zahorsky	Interstate M. J., 22: 57.	15 mo.	F
17	1915	Whipham	Brit. J. Child. Dis., 12: 321.	18 mo.	F
18	1915	Whipham	Brit. J. Child. Dis., p. 11.	12 yr.	F
19	1916	Frank and Polak	Nederlandseh. Tijdschr. v. Geneesk., 52: 2172.	2 yr.	F
20	1918	Base	J. A. M. A., 70: 287 (Feb. 2).	15 yr.	M
21	1919	Eyster and Middleton	Am. J. Dis. Child., Feb., 1920, p. 131.	2 yr.	M
22	1912	Rohmer	Ztschr. Exp. Path. and Ther., 1912m., 426	8 yr.	F
23	1912	Rohmer	.....	5½	F
24	1913	Hecht	Erg. inn. Med. and Kinderheilk, 1913, 392.	3 yr.	F
25	1913	Hecht	Erg. inn. Med. and Kinderheilk, 1913, 392.	3 yr.	M
26	1913	Hecht	Erg. inn. Med. and Kinderheilk, 1913, 392.	5 yr.	M
27	1913	Hecht	Erg. inn. Med. and Kinderheilk, 1913, 392.	15 yr.	M
28	1913	Hecht	Erg. inn. Med. and Kinderheilk, 1913, 392.	9 yr.	M
29	1913	Hecht	Erg. inn. Med. and Kinderheilk, 1913, 392.	10 yr.	M
30	1915	Whipham	Brit. Jr. Dis. Child., 12–1911.	(2 yr.) (2 mos.)	F M
31	1919	Brown	Arch. Int. Med., 24: 458.	11 yr.	
32	1923	Seham	Not published	9	F

TABLE 16

Disease	Nature of block	Character	Duration	Ventricular rate	Termination	Stokes Adams syndrome	Electrocardiogram
Rheumatism	?	Recurrent	3 mo.	35	.....	Present	A
Congenital	Complete	Continuous	4 yr.	50–70	Death	Present	A
Congenital	Complete	Continuous	18 mo.	50–70	.....	Present	A
Congenital	Complete	Continuous?	1 yr.	28–44	Death	Present	A
Diphtheria	?	Continuous?	3 days	18–40	Death	Present	
Congenital	Complete	Recurrent	11 yr.	34	.....	Present	?
Congenital	Complete	Continuous	.....	40–50	.....	Absent	A
Diphtheria	Complete	Recurrent	5 days	29–38	Death	Present	A
Diphtheria	Complete	Continuous	3 days	46–54	Death	Absent	A
Diphtheria	Complete	Continuous	5 days	34–48	Death	Absent	A
Diphtheria	Complete	Recurrent	3 days	5	Recovery	Present	A
Cardiac tumor	Complete	Recurrent	18 mo.	28	Death	Present	A
?	Complete	Continuous	3 yr.	40	.....	Present	P
Diphtheria	Partial, late. comp.	Continuous	6 mo.	30–60	Recovery	Present	P
Congenital	Complete	Continuous	1 mo.	20–32	.....	Present	A
Congenital	Complete	Continuous	14 mo.	50	.....	Present	A
Bronchitis	Partial	Continuous	8 mo.	56–64	.....	Absent	*P
Congenital?	Complete	Continuous	6 yr.	40–64	.....	Absent	P
Pyogenic	Complete	Continuous	.....	42–48	.....	Absent	?
Congenital.....	Complete	Continuous	.....	37	.....	Absent	P
Pyogenic?	Partial	Continuous	2½ yr.	58	.....	Absent	P
Laryng. diphtheria	Complete	.....	3 days	62–30	Death	.....	P
Laryng. diphtheria	Complete	.....	3 days	42	Death	.....	P
Measles	Complete	Recurrent	1 mo. (?)	260	Recovery	.....	P
Diphtheria	Complete	.....	4 mo. (?)	.....	.....	.....	P
Measles, influenza	Complete	.....	.....	63	.....	.....	P
Chr. hydrocephalus	Complete	.....	8 days (?)	46	Recovery	.....	P
Measles(?)	Complete	.....	3–4 yr.	36–40	.....	Present	P
Lues	Partial	.....	.....	.....	.....	.....	P
Cong. heart P. St.	Complete	.....	?	48	?	.....	P
Rheumatism	Complete	Continuous	3 yr.	58–64	Recovery?	Absent	P
Cong. heart P. St.	Partial	Continuous	1 yr.	50–54	?	Absent	P

TABLE 17.—CASES OF AURICULAR FIBRILLATION IN CHILDREN

Author	Date	Age	Cause	Ass. signs	Consequent course	Electrocard.
Sutherland.....	1913	5 yrs.	Rheumatism	Decompensation	Died P.M. Done	Polygraph
Ehrenreich.....	1914	11 yrs.	Rheumatism	Dilatation decompensation. Heart murmur.	Died	Electro not published
Nadel.....	1914	11 yrs.	Rheumatism repeated	Decompensation	Died	P-R. 2 sec.

Auricular Fibrillation.—Auricular fibrillation is usually the last stage of auricular degeneration. It is very rare in childhood because it takes such a long period for the development of this condition. Only three cases have been recorded in the literature in children under 15 years.

Table 17 shows the cases that have been graphically recorded. P is absent in all leads. The ventricular complexes Q-R and S-T occur irregularly as to height, form and rate. The absence of the regular auricular contraction is explained by the fact that the individual muscle fibers contract independently of one another so that some fibers are in a state of contraction while others are relaxed. The variations of R are due to distortion caused by superimposition of small waves representing auricular activity.

The Heart in Contagious Diseases.—In diphtheria the electrocardiograms seem to be of some value for diagnosis and prognosis. In the other contagious diseases very little study has been made and the few investigations up to the present time have yielded inconstant and inconclusive results.

Diphtheria.—Rohmer, in 1911, was the first to record the heart action in diphtheria by means of the electrocardiograph. In six cases with slightly impaired heart action, in which myocarditis had been diagnosed clinically, he found the electrocardiograms to be normal with well developed waves.

In five cases of laryngeal diphtheria that ended fatally (Lead I only) he found the auricular wave absent in the later stages and the ventricular wave broadened at the base and split. He also noted the presence of a heart-block both partial and complete. In several instances, just before death, the ventricular complexes were very abnormal and so irregular in outline and height that an interpretation was impossible. There were several split and diphasic R-waves in the moderately severe cases.

Rohmer thus assumes that in diphtheria the electrocardiogram reveals disturbances of the impulse conduction which cannot be disclosed otherwise.

Hecht, in 1913, examined 42 cases of diphtheria. Six of these exhibited sinus arrhythmia, a normal proportion and therefore without any clinical significance. In two of the 42 cases R was very low; it was split in seven instances. A split P was observed four times. Since P is never split in the electrocardiogram of normal hearts, this occurrence might be interpreted as indicating damage of the auricular muscle or even damage of the walls caused by diphtheria toxin. In none of the 42 cases was the transmission time markedly reduced.

McCullough in his study of 80 cases of diphtheria found that the electrocardiogram showed evidence of disturbance either in the intrinsic conducting system or in the heart muscle in 19 cases.

Of these, four showed a heart-block of the auriculoventricular type, two were extra-systoles, one ventricular and the other

auricular. In six there was a disturbance in conduction, in one a left ventricular preponderance. McCullough concluded that the electrocardiograph was especially valuable for prognosis.

Scarlet Fever.—Hecht was the first to study the heart in scarlet fever. In 10 cases out of 59 studied, he found sinus arrhythmia, which is not unusual at that period of childhood. He found a tachycardia over 150 beats per minute in 9 cases; however, none was a true paroxysmal tachycardia. In 15 cases there was a slight increase of the P-R interval. In a large number of the cases the S in Leads II and III was deeper than R_1 which is not a normal sign. In seven cases he noticed a split P. In one, P was absent during the entire course.

Measles.—Hecht examined only three children convalescing from measles. All three records exhibited severe arrhythmia with pulse periods ranging from 29 to 50 ($\frac{1}{50}$ of a second).

Miscellaneous Diseases.—Typhus Abdominalis.—Hecht cited the results of electrocardiographic studies in one case of typhus abdominalis, in a boy of 12 years of age. In this instance the bradycardia was very pronounced. The pulse period measured 32 (in $\frac{1}{50}$ of a second), and the P-R interval, 0.16 second.

Spasmophilia.—Because of frequent sudden deaths it has been supposed that the heart in spasmophilia might show some pathological evidence.

Morgenstern, in his desire to discover a relation between this disease and the activity of the heart muscle, took electrocardiographic records of 15 nurslings and two children below three years of age, with symptoms of spasmophilia. He comes to the conclusion that the electrocardiograms of children in spasmophilia seem to be characterized by a well developed R-wave (about equal to S) and a steep pointed T. However, he reserved his final opinion as to an involvement of the heart muscle in this condition. Hecht reported electrocardiographic findings of three cases of spasmophilia. In none of his cases could he find results associated with vagotonia.

Case 1.—A girl, six years old, has permanent carpopedal spasms. The electrocardiogram showed a surprisingly small R in Lead I. The P-R interval was 0.12 second.

Case 2.—A girl, 13 years old, with laryngospasms and expiratory apnea. R_1 was only slightly larger than T. Here too the transmission time of the auricle was 0.12 second.

Case 3.—The third case was a four months old child, with typical tetanus and convulsive attacks. The pulse period was found to be 25, the P-R interval 0.15 second. Unfortunately other data were omitted.

The author has examined nine cases of spasmophilia. All showed positive Chvostek or Weiss signs, and gave histories of restlessness and convulsions. Nothing definite or abnormal could be found in the tracings of these cases. There was a slight irregularity in one case (sinus arrhythmia). Three cases showed rather high ventricular complexes and in two cases P_3 was inverted. But all these data are

consistent with a normal electrocardiogram during the respective periods of childhood and are of no significance.

A study of two cases of infectious jaundice, of five cases of nephritis, five of meningitis, 16 of pneumonia revealed nothing unusual.

Investigation of several cases of alimentary disturbance and decomposition disclosed no constant peculiarities. In one child that could not take any food the P-R interval became slower as the child became worse and T in Leads II and III, and R in Lead I became much higher.

Ten cases of lues, one of diabetes mellitus, and one of diabetes insipidus showed nothing abnormal. In adults with a goiter there is supposed to be a rather high T in all leads and an arching in the ascending limb of the final wave. In 10 cases of physiologic goiter at from 10 to 14 years of age, the high T was quite constant but the arching was not sufficiently uniform to be of any importance. In several tracings occurred some fine oscillations probably due to the coarse tremor. Two cases showed a rather high T, which can be explained on the basis of the thyroid treatment, which probably caused hyperventricular action.

Heart of the Fetus.—Up to the present time no permanent electrocardiograms of the heart of the fetus have been obtained. Foa refers to Cremer's unsuccessful attempt (1910) to secure records of the fetus *in utero*. Cremer introduced one silver electrode into the rectum and placed another on the abdominal wall. Foa, in 1911, attempted to study the electrocardiograms of three fetuses *in utero* at eight months of age. He secured the records of both the child and the mother by placing one electrode on the abdomen and the other within the vagina in contact with the uterus. He shows one tracing which is difficult of interpretation. This subject needs further investigation.

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TABLE 18

Case	Age	Weight	Heart size, centimeters	X-ray, centimeters	Clinical diagnosis	Electrocardiograph diagnosis
1	6 mo.	6835 gm.	3 × 6	2½ × 6½	Pulm. stenosis P.M. & pat. ductus arteriosius.	Rt. vent. preponderance.
2	4 yr.	35 lb.	3 × 7	2½ × 8	Pat. ductus arteriosus.	No rt. vent. preponderance.
3	6 yr.	35 lb.	3½ × 7	3 × 9	Pulm. stenosis & pat. vent. septum.	Rt. vent. preponderance.
4	3 yr.	27 lb.	1½ × 6	None taken	Pat. vent. septum, hypospadias, webbed toes.	No vent. preponderance.
5	18 mo.	27 lb.	1½ × 5½	2 × 5½	Foramen ovale.	Rt. vent. preponderance.
6	15 mo.	6625 gm.	1½ × 5	None taken	Mongolian idiocy, pat. vent. septum.	Lt. vent. preponderance.
7	8 mo.	10 lb.	3 × 7	3 × 6	Pat. vent. septum with pulm. stenosis.	Rt. vent. preponderance.
8	8 mo.	18 lb.	2½ × 6 3 × 6	None taken	Pat. ductus arteriosus.	Lt. vent. prep. leads. Exaggerated amplitude in all.
9	8 yr.	55 lb.	2½ × 6	2 × 6	Pat. auricular or vent. septum.	No vent. preponderance.
10	3 yr.	28 lb.	2 × 6	2 × 6	Pat. auricular or vent. septum.	No vent. preponderance.
11	2½ yr.	32 lb.	2½ × 7	2½ × 7	Pat. auricular or vent. septum.	No rt. vent. prep.
12	3½ yr.	42 lb.	2½ × 7	None taken	Pat. auricular or vent. septum.	Rt. vent. prep.
13	3½ yr.	29 lb.	3½ × 7	3 × 8	Pulm. stenosis, pat. vent. sept.	Electro. diag.
14	1½ yr.	23 lb.	2 × 6½	None taken	Patent septum auricular.	Rt. vent. prep.
15	4 yr.	33 lb.	2 × 6½	2 × 7	Patent septum auricular or ventricular.	Rt. vent. prep.
16	2 yr.	27 lb.	3½ × 7	4 × 7	Transposition of the great vessels.	Rt. vent. prep.

TABLE 19

Case clinical diag.	Electrocard. diag.	1	P 2	3	1	Q 2	3	1	R 2
1. Pulmonary stenosis & patent ductus.	Rt. vent. hypertrophy.	0.15	0.2	0.1	0.0	0.0	0.0	0.3	1.4
2. Patent ductus arteriosus.....	No. rt. vent. hypertrophy.	0.2	0.2	0.1	0.0	0.2	0.2	0.9	1.5
3. Pulmonary stenosis & ven. septum.	Rt. vent. hypertrophy.	0.2	0.3	0.1	0.0	0.3	0.3	0.4	1.8
4. Patent septum or ventricu. or auric. hypospadias, webbed toes.....	No vent. hypertrophy.	0.1	0.2	0.0	0.0	0.0	0.0	0.9	0.7
5. Foramen ovale.....	Rt. vent. hypertrophy.	0.0	0.1	0.1	0.0	0.0	0.2	0.2	0.6
6. Mongolian idiocy, auricular or vent. septum (patent).	No rt. vent. hypertrophy, left vent. hyper.	0.0	0.3	0.0	0.0	0.0	?	0.2	0.3
7. Patent vent. sept. with pulmonary stenosis.	Both vent. hypertrophied, impaired intravent. conduction (esp. rt.).	0.3	0.3	0.1	0.0	0.0	0.0	1.0	0.9
8. Patent ductus arteriosis.....	Lt. vent., hypertrophy.	0.05	0.05	0.02	0.05	0.0	0.0	1.0	0.6
9. Patent auricular or vent. sept....	No vent. hypertrophy.	0.1	0.1	0.2	0.0	0.0	0.0	0.4	1.2
10. Patent vent. or auric. septum....	No vent. hypertrophy.	0.1	0.1	?	0.0	0.0	?	0.6	0.5
11. Auricular or vent. patent septum.	No hypertrophy of right ventricle.	0.1	0.15	0.1	0.15	0.0	0.0	0.6	0.3
12. Patent septum auricular or vent..	Rt. vent. hypertrophy.	0.1	0.1	0.09	0.0	0.15	0.3	0.5	1.9
13. Pulm. stenosis & patent vent. septum.....	Rt. vent. prep.	0.3	0.4	0.15	0.1	0.3	0.3	0.3	0.6
14. Patent auric. or vent. septum....	Rt. vent. prep.	*0.2	0.2	0.3	0.0	0.1	0.3	0.3	0.8
15. Patent auric. or vent. septum....	Rt. vent. prep.	0.15	0.15	0.1	0.0	0.1	0.2	0.2	0.7
16. Transposition of great vessel.....	Rt. vent. prep.	0.15	0.3	0.2	0.1	0.1	0.0	0.1	1.5

TABLE 19.—(*Continued*)

S			T								
3	1	2	3	1	2	3	PQ	QS	ST	VP	Rate	Remarks
1.5	1.1	0.3	0.3	0.3	0.4	0.1	0.14	0.05	0.20	−20	161	Deep R_2R_3, P_3 inverted.
1.0	0.1	0.4	0.3	0.5	0.7	0.2	0.14	0.04	0.30	+2	71	
1.9	0.6	0.8	0.0	0.2	0.6	0.6	0.18	0.04	0.26	−21	106	
0.1	0.0	0.1	?	0.25	0.25	0.0	0.15	0.03	0.27	+8	103	Split S_3 & R_3.
0.6	0.3	0.1	0.0	0.1	0.02	0.05	0.13	0.02	0.30	−7	110	
0.1	0.2	1.5	0.3	0.0	0.3	0.0	0.12	0.18	0.20	+2	136	Deep S_2.
0.2	1.1	0.6	0.5	0.4	0.6	0.4	0.18	0.10	0.20	−10	137	Split R_3 S_3.
0.3	0.2	0.4	0.4	0.05	0.3	0.2	0.13	0.07	0.28	+9	135	Split S_3.
0.1	0.2	0.1	0.0	0.2	0.3	0.2	0.13	0.03	0.29	+11	96	Broad P 1–2–3.
0.2	0.2	0.3	?	0.2	0.1	?	0.12	0.03	0.25	+2	105	
*0.2 & 0.4	0.3	0.5	0.2	0.6	0.6	0.2	0.15	0.07	0.22	+1	118	Split R_3 & S_3. T_3 inverted, P_1 very broad.
2.2	0.6	0.1	0.0	0.5	0.5	0.15	0.18	0.03	0.22	−23	115	Very high R_2R_3. Deep S_1.
1.8	1.0	0.2	0.1	0.4	0.2	0.15	0.12	0.05	0.22	−24	...	P_2 notched, $S_1 - R_2$ notched & thickened, T_3 inverted.
1.7	1.7	0.1	0.2	*0.4	0.3	0.6	0.14	0.07	0.22	−29	...	P sharp and pointed. T_2 notched & flattened. T_3 inverted.
0.8	0.6	0.3	0.1	0.2	0.4	0.2	0.17	0.03	0.25	−9		
3.0	1.2	0.2	0.2	0.3	*0.1	*0.3	0.12	0.07	0.18	−39	...	R_2 notched. T_3 inverted.

TABLE 20.—PERCENTAGE OF SINUS ARRHYTHMIA (Normal Child)

Age	Friberger	Hecht	Author
Newborn	....	3.4	3.0
1–2 yr	....	2.8	2.0
2–5 yr	....	6.0	0.3
5–6 yr	85.7		
6–13 yr	....	8.4	47.0

TABLE 21.—REVIEW OF 17 CASES

Reported by	Date	Age	Sex	Predisposing factors	Age when paroxysms began, yr.	Number of paroxysms	Duration of paroxysms	Normal pulse
Buckland, F. O.	1802	11	♀ M.	Measles; neurotic temperament.	5	Numerous; two attacks observed.	12 hr. to 10 days.	84 to 96
Herringham, W. E.	1898	11	♀ M.	Scarlet fever during infancy; tonsillitis; constipation.	5	Seven in 10 mo.	18 hr. to 13 days.	80 to 96
Merklen, P.	1901	13	♀ M.	.....	Not stated.	Occasional.	12 hr. to 8 days.	80
Hay, John	1907	6	♂ F.	Delicate constitution.	6	Frequent; almost continuous for 6 mo.	Few seconds to 10 days.	84
Hume, Wm. E.	1913	6	M. ♀	Occurred during convalescence from diphtheria after antitoxin treatment.	6	Numerous on 41st and 51st days of illness	Short and long periods.	88
Kidd, Percy	1914	4½	♂ F.	Measles.	2	About once each month; frequent during last 6 mo.	Few minutes, later almost continuous.	80
Hutchinson, R. and Parkinson, J.	1914	2¾	F. ♂	No previous illness; well nourished.	2¼	Four in 5 mo.	12 hr. to 12 days.	64 to 80
Lewis, Thomas	1914	3 mo.	.....	.....	3 mo.	.....	Several hours.	.....
Sutherland	1914	8	F. g.	.....	.....	.....	.....	105(?)
Sutherland	1914	6	F. g.	.....	.....	.....	.....	.....
*Koplik	1915	22 mo.	M. b.	Influenza, angina and bronchopneumonia, rachitis.	22 mo.	10 in 1 yr.	Abruptly.	104
*Koplik	1915	10	b. M.	Measles.	.....	Every 5 days.	15 days.	?
Koplik	1916	3	F. g.	At 3 mo. first noticed palpitation.	.....	Many.	Abruptly.	?
Hart, T. S.	1917	10	M. ♀	.....	9	.....	.....	.....
Brown	1917	3½	F. ♂	Gastro-intestinal disorders and malnutrition during infancy.	During 1st yr.	Usually every 3 or 4 days.	2 to 36 hr.	90 to 112
Strong*	1919	9	F. g.	Diphtheria? Measles.	9	.....	3 mo.	.....
Strong*	1919	5	F. g.	Chickenpox? Tonsillitis?	5	Numerous.	Persistant.	.....

* Auricular tachycardia.

OF PAROXYSMAL TACHYCARDIA

Pulse during paroxysm	Paroxysm begins	Paroxysm ends	Accompanied by	Subsequent course	Graphic records
200 to 215	Abruptly with arrhythmia.	During sleep.	Pallor; dizziness; rapid breathing; low fever.	Probable recovery.	None.
200 to 256	Abruptly; often with sudden movement.	Always during sleep.	Languor; slight cyanosis; cardiac dilatation; enlargement of liver; jugular pulsation.	Recovery.	None.
220	Abruptly.	Abruptly; often with coughing and hemoptysis.	Dyspnea; cardiac dilatation; epigastric hyperesthesia; hemoptysis.	Unknown.	None.
182 to 230	Abruptly; sometimes with vomiting.	Abruptly; often with periods of arrhythmia.	Pallor; listlessness; pulmonary edema cardiac dilatation; hepatic enlargement; jugular pulsation.	Recovery.	Polygram; ventricular venous pulse during paroxysms; numerous auricular extrasystoles as attacks subside.
225	.....	.....	Collapse; nausea and vomiting; cardiac dilatation.	Recovery.	Polygram; tachycardia apparently of nodal origin; extrasystoles precede paroxysm.
240	Abruptly; with momentary collapse.	Abruptly; sometimes after vomiting.	Cardiac dilatation; hepatic enlargement; general anasarca; dyspnea.	Fatal termination; probably from malignant endocarditis.	None.
160 to 245	Abruptly; often with momentary collapse.	Abruptly; once after defecation; often with arrhythmia.	Vomiting; cardiac dilatation; slight edema, enlarged and pulsating liver; partial suppression of urine; jugular pulsation.	Recovery.	Polygram; ventricular venous pulse during paroxysms; electrocardiogram R modified by inverted P; nodal origin. (?)
270 to 290	.....	.....	.....	.....	Electro-cardiogram; inverted P between R and T; probably auricular tachycardia.
280	.....	.....	Cardiac asthma; dyspnea; cyanosis; enlarged liver; pulsus alternans.		
250 to 390	.....	.....	Triple or galloping rhythm; pericarditis.	?	
224 to 280	.....	.....	Edema; cyanosis; dyspnea.	?	Auricular tachycardia.
200 P R 54 irregular	.....	.....	Vomits; palpitation; cyanosis; distress.	3 yr. well.	Auricular flutter of heart-block 2:1 ventricular extrasystoles.
240	.....	.....	Palpitation; dyspnea comfortable.	.....	250″ P cannot be seen. Auricular tachycardia.
.....	.....	.....	.....	.....	Electrocardiogram.
180 to 200	Abruptly; no premonition.	Abruptly; with sense of relief; often during sleep.	Slight pallor; lessened activity; jugular pulsation.	Reduction in frequenty and severity; of paroxysms.	Electrocardiogram inverted P with beginning of T-wave; auricular tachycardia.
240	.....	.....	Pale; nausea; anorexia low fever; heart size 1.5 × 8 cm.	Recovery.	Electrocardiogram.
170 to 180	.....	.....	Pale; fatigue; heart 3 × 7.5 cm. Respiration 44.	No recovery.	Electrocardiogram.

CHAPTER LXXII

ACQUIRED DISEASES OF THE HEART

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PERICARDITIS

Acute Pericarditis

Frequency and Age Incidence.—Baginsky* found pericarditis among 4500 sick children either clinically or at post-mortem 66 times—an incidence of 1.5 per cent. Of these 66 cases, 20 occurred during the first year of life, and 33 between the first and ninth years. Thirty-eight occurred in boys, 32 in girls.

The statistics given by E. Weill† show pericarditis to be less frequent—42 cases among 6000 girls admitted to the hospital, 0.6 per cent.

During the first year of life, pericarditis when present is almost invariably purulent and is either part of a pyemia or is secondary to pulmonary disease. In later childhood rheumatism is the commonest cause, as is well shown by the following table taken from G. F. Still‡:

AGE INCIDENCE OF RHEUMATIC PERICARDITIS IN 53 CASES

Age:	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12
No: of Cases.	0	0	1	2	4	7	12	4	10	7	4	2

In this series of 53 cases, 33 were males and 20 females.

It is particularly difficult to gather statistics on this disease because autopsies have shown that it is very frequently overlooked during life, its occurrence not being suspected even when the case is under competent supervision.

Etiology.—Acute pericarditis is rarely a primary disease; it is almost always found secondary to the following conditions:

1. Rheumatism.—Rheumatism causes the majority of cases of pericarditis in children. In fact, this complication of rheumatism is much more common in children than in adults. It may appear in combination with joint inflammation, angina or chorea. It is usually associated with endocarditis. So-called primary cases of pericarditis in children are found, as a rule, to have been due to rheumatism.

2. Pleuropneumonia.—The close relationship of the pericardium and the pleura explains the frequency of pericarditis as a complication

* Berlin. Klin. Wochenschr., xxxv (1898), p. 1053.

† Traité Clinique des Maladies du Coeur Chez les Enfants, Paris (1895).

‡ Common Disorders and Diseases of Childhood, London (1912).

of inflammatory conditions of the lungs and pleura. This variety of pericarditis is especially common in the earlier years of life—before the sixth year.

3. Septicemia and Pyemia.—The pericardium may be involved in any septic process. To this group belong the cases of pericarditis in the newborn, where infection enters through the umbilical cord. Von Reuss* reports a case in an eight day old infant in which the pericardial inflammation was the only metastasis of a meningitis due to Bacillus Coli. Baginsky describes a purulent pericarditis in an infant 10 days old. In older children this form is seen in the course of osteomyelitis, abscess, impetiginous skin lesions, stomatitis, etc.

4. Infectious Diseases.—Here belong the inflammations of the pericardium seen in diphtheria, measles, varicella, variola, typhoid, mumps, and especially scarlet fever. Here also properly belongs the insidious form described by Still as occurring with chronic polyarthritis, enlarged lymph nodes, and large spleen.

5. Tuberculosis.—Involvement of the pericardium in tuberculosis is less common in children than in adults. In a series of 51 cases collected by Rousseau,† 18 were under the age of 15 years, and only 2 were under 5 years. Baginsky classifies 11 of his 66 cases of pericarditis as tuberculous, but of these 11, only 6 showed actual tubercle tissue or caseation in the pericardium. The inflammation may arise as a part of a general miliary tuberculosis or may be a direct extension from tuberculous lymph nodes or lung.

6. Pericarditis from Extension.—Inflammation of adjacent structures may set up disease in the pericardium. Here belongs pericarditis secondary to osteomyelitis of the ribs or sternum; to mediastinitis, etc. In rare instances, direct trauma may be a cause, as in a case quoted by Nobécourt‡ of a 10 year old boy who was struck on the chest and subsequently developed pneumonia and a streptococcus pericardits.

Pathology.—Pathological evidence of pericardial inflammation may consist in a deposition of fibrin on the visceral or parietal pericardium, or the process may go on to exudation, which may be serous, seropurulent, purulent, or hemorrhagic.

In the rheumatic variety the serosa is dull and hyperemic, and fibrinous deposits are found at the base of the heart. Fluid exudate may or may not be present. When present, it is, as a rule, small in amount, 100 to 150 c.c., and serous in nature. The exudate may be resorbed and the fibrin disappear, or organization may take place with the formation of adhesions between the pericardial leaves. There is at the same time involvement of the myocardium.

When the inflammation is due to tuberculosis there may be a similar serofibrinous exudate, or else miliary tubercles and caseation may be found. Baginsky warns against mistaking for tubercles small nodular deposits in the pericardium which he considers due to rheumatism.

* Die Krankheiten des Neugebornen, Berlin (1914).
† Paris Thesis (1882).
‡ Cardiopathies de l'Enfance, Paris (1914).

The exudate in cases due to the tubercle bacillus is often hemorrhagic in character.

In the purulent type the exudate varies from cloudy serum to thick creamy pus. The latter is especially frequent when the pneumococcus is the causative organism. The deposits of pus and fibrin may be very thick causing the heart to appear as a grayish green shaggy mass.

Symptoms and Physical Signs.—There is no disease of infants and young children which is more easily overlooked than pericarditis, and no lesion which so often appears at the autopsy table, to the surprise of the unsuspecting physician. Even in cases where it is particularly sought for, the onset and course of the disease may be so insidious that it is completely overlooked. In very young infants the diagnosis during life is often impossible, since there need be no clinical signs whatever pointing to an involvement of the pericardium, while at post-mortem the most marked changes may be present. In young children in whom the disease usually complicates pleuropneumonia, the general symptoms of the primary infection become more marked, the temperature becomes septic in type, the prostration profound, the pulse rapid and feeble. Occasionally a friction rub may be heard, but often this is absent, and even the proper delineation of the cardiac outline is impossible owing to the confusion with the dulness caused by pneumonic consolidation, pleural thickening and effusion. One may suspect pericarditis in such cases when in the course of a severe pneumonia the heart sounds suddenly become very much diminished in intensity, without a coincident weakening of the pulse. In young children the apex impulse need not be obliterated even with a marked effusion, as in a case recently under observation, where a two year old child suffering from interlobar empyema ran a septic temperature with rapid pulse, but with perfectly palpable apex impulse and fairly audible cardiac sounds with no murmurs or friction sounds. At autopsy, the heart was found covered with a shaggy thick mass of fibrin, and the pericardial sac contained about 30 c.c. of thick pus.

In older children, especially in those suffering from the rheumatic form of the disease, the diagnosis can more often be made. The disease here often sets in with precordial distress and substernal pain. The child looks very pale and ill. Fever is usually present. There may be annoying cough, restlessness and often vomiting. The pain may be extremely severe; localized to the heart region or radiating to the shoulder or neck. Dyspnea is marked, even when there is no sign of effusion, the respirations being short, rapid and restrained. The pulse is rapid and the heart action tumultuous. Auscultation reveals the characteristic friction sound—a grating or shuffling to and fro sound, heard usually first over the base of the heart, increased by pressure of the stethoscope and by having the child bend forward. The sound is not confined either to diastole or systole; it is usually not transmitted but spreads over the precordium as the exudate increases. According to Hutinel* the loudness of the friction sound varies with

*Les Maladies des Enfants, Paris (1909).

the organism causing the exudate—it is soft in streptococcus and staphylococcus inflammations, rough in the pneumococcic and rheumatic.

If the process goes on to the exudation of fluid, there is usually a gradual disappearance of the friction sound, while the pain becomes less severe. The area of cardiac dulness increases rapidly. The characteristic triangular area of dulness is not, as a rule, present in children, except in moderate sized effusions (Holt). In large effusions the dull area is more or less circular in outline, or follows the outline of the heart, overlapping it so as to extend several centimeters outside the right sternal border and similarly to the left of the nipple line (Baginsky). In rare instances, the dulness extends outward to the axilla. Obliteration of the cardio-hepatic angle may occasionally take place, but the sign is not as constantly present in childhood as it is in adult life. Distinct bulging of the chest wall may appear, and with it a sense of undulation may be transmitted to the examining hand. As the dulness appears the cardiac impulse becomes less marked and the heart sounds diminish in loudness. In large effusions an area of dulness and bronchial breathing appears on the left side posteriorly below the scapula, as a result of compression of the left lung.

As the signs of effusion appear the symptoms of cardiac embarrassment become more marked. Dyspnea increases and may become so extreme that the knee-chest position is assumed by the child (Hutinel). The veins of the neck become distended and slight edema and cyanosis of the face may appear.

The tuberculous variety may run an entirely latent course, presenting no signs or symptoms whatever.

Course and Prognosis.—The course and outcome of acute pericarditis depend on the type of infection and the character of the primary disease. The purulent variety is almost invariably fatal. The rheumatic form may go on to apparent recovery, though it usually leaves evidence of a considerably damaged heart. When, as so often happens, the disease occurs in a child whose heart has been previously crippled by endocarditis, the prognosis must be considered serious. According to de Gassicourt, pericarditis is the most serious complication of rheumatism in the child and the one which most frequently leads to death.

The figures given by Still (*loc. cit.*) are of interest in this connection: Of 53 cases of rheumatic pericarditis only one made an absolutely complete recovery. Nine cases recovered to the extent of having lost all acute symptoms when seen several weeks after the illness. Of the remaining 43 cases, nine died two weeks after the onset; four within a month: five within a few weeks; seven within four months. Of the remainder all died within a few months excepting two that died one and two years after the acute attack. Factors influencing the prognosis are: Amount of dilatation, presence of pulmonary consolidation, pleurisy.

In cases with large effusions one must bear in mind that sudden death may occur.

Diagnosis.—The difficulty of diagnosing acute pericarditis has already been alluded to. Dry pericarditis can be recognized by the friction rub. To differentiate this sound from endocardial murmurs the following points may be useful: Friction is apparently more superficial and nearer to the ear; it does not strictly correspond to any one phase of the cardiac cycle; it is inconstant, often disappearing and reappearing again; it is influenced by posture and by pressure of the stethoscope.

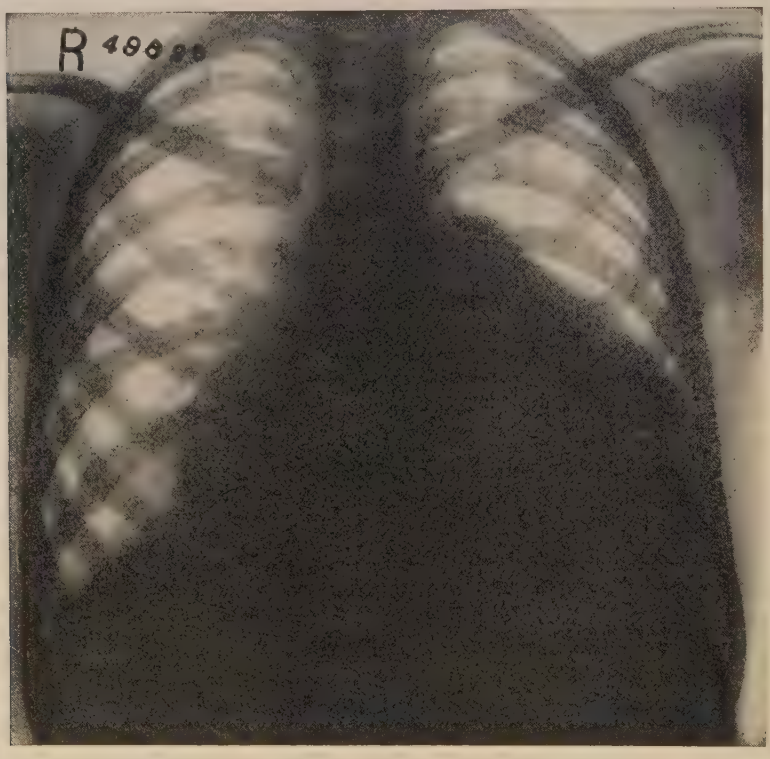

FIG. 118.—Radiogram: Pericarditis with effusion.

From pleural friction the pericardial sound must be differentiated by its relation to phases of respiration.

The physical signs of pericardial effusion often closely resemble those of cardiac dilatation. The heart, however, rarely enlarges to as great an extent in as short a time. In effusion, the apex beat is less easily felt. On changing the position of the child, cardiac dulness will be found to shift much more readily in effusion than in dilatation. Signs of compression of the left lung cannot be relied upon to differentiate the two conditions, since these signs have been present in cases where post-mortem no effusion but only a large heart has been found. One should also remember that in dry pericarditis

there may be and often is a marked enlargement of cardiac dulness due to dilatation and not to exudation (Still).

In recent years the Roentgen ray has greatly aided in the diagnosis of effusion. A characteristic radiogram of a pericardial effusion is shown in Fig. 118. If daily fluoroscopic examinations are made of a case in which pericardial effusion is developing, the observer will note a rapid increase in the size of the cardiac shadow. A rapid enlargement to the right is especially characteristic. The typical outline of the heart is obliterated and in its place we find a somewhat flask-shaped shadow. The lateral portions of the silhouette are distinctly convex; the shadow of the vessels is broadened, and finally in large effusions the transverse diameter of the shadow exceeds the vertical, a condition which only very rarely obtains in the hypertrophied heart. Under the fluoroscopic screen the pulsation of the various portions of the heart become indistinct and the observer sees only a systolic impulse transmitted to the shadow as a whole.* In cases of suspected effusion the chest should be viewed in the lateral positon also, since in rare instances the pericardial effusion is sacculated and lies behind the heart (Hutinel).

Treatment.—From the prophylactic standpoint we are able to prevent pericarditis only by the early recognition of its causative agents, especially rheumatism. Children who have attacks of arthritis, chorea or frequent angina should be particularly protected against taking cold. Hypertrophied tonsils in such cases are a serious menace and should be removed. Mild attacks of arthritis or myalgic pain should not be made light of, but should be energetically treated with salicylates.

When pericarditis is present, the child should at once be put to bed. The diet should be light and easily digestible—fluids, cereals, eggs, etc. An ice bag should be kept over the heart. The bag should be small and only partly filled so as not to lie heavily on the chest. It may be supported by a strip of gauze, so as to hang from about the neck and thus be retained in place when the child assumes a semi-upright position. This posture may be found best especially when there is much dyspnea.

In the rheumatic variety of pericarditis, salicylates must be administered in large amounts—sodium salicylate in doses of 15 to 25 gr. a day to a child of five years, and double this dose to a child of 10. The drug should be given with double the dose of sodium bicarbonate every two to three hours. To children who do not tolerate this form of salicylate, aspirin or novaspirin may be given. Where these drugs are vomited, administration by rectum is advised—15 gr. in 4 oz. of water twice a day (Kerley).

For pain, discomfort, restlessness, or insomnia, bromides or morphin and its derivatives should be employed. To young children paregoric may be given; to older ones codein ($\frac{1}{6}$ to $\frac{1}{4}$ gr. for

*Dietlen, H. in Rieder and Rosenthal's Lehrbuch der Roentgenkunde, Leipzig (1913).

a child four to six years old; ¼ to ⅓ gr. for a child 6 to 10 years old); in children approaching puberty, morphine in small doses.

In the treatment of acute pericarditis one must not lose sight of the fact that there is more or less involvement of the myocardium present and that the heart muscle itself needs attention. If sedatives do not reduce the pulse rate, digitalis should be exhibited. (See treatment of myocardial insufficiency under Endocarditis.)

If a purulent exudate is suspected, or if the exudation persists in spite of treatment and the child appears to be losing ground, exploratory puncture and aspiration of the pericardium may be resorted to. This is best performed by entering the pericardium from below. The child should be in a semi-reclining position. The operator's left fore finger is placed on the xyphoid and the needle is inserted just below this in the mid-line. It is directed upward and backward as if to pass along the posterior border of the sternum. In a child of five years the needle must be inserted to a depth of about 4 cm.*

The advantages claimed for this method are that the mammary artery and the pleura are avoided and there is little chance of wounding the heart. The contraindications are a tympanitic abdomen and a funnel-shaped chest.

All cases before being punctured should be examined with the Roentgen ray.

If pus is obtained, the treatment is surgical.

Chronic Pericarditis

Chronic pericarditis especially in its most marked form, so-called adherent pericardium, is justly regarded as the most serious complication of cardiac disease in childhood. In the words of Fisher† "we may say that adherent pericardium is the form of chronic heart disease most to be feared in children, while in adults valvular disease is of far greater consequence."

Etiology.—The causes of chronic pericarditis are virtually the same as those of the acute variety, which have already been discussed. By far the most important are rheumatism and tuberculosis. Chronic pericarditis may follow directly upon an attack of acute pericardial inflammation; it may be the result of numerous acute attacks; or it may develop insidiously in the course of a chronic endocarditis or tuberculosis. In the last mentioned type the condition may easily be overlooked, and as in the acute form, may only be discovered at the post-mortem examination.

The disease is relatively frequent in early life. Of 30 cases collected by Morel-Lavallee,‡ 18 were in individuals under 20 years of age. Cerf§ in 43 autopsied cases found 18 under 20 years of age.

* Marfan, Gaz. Med. de Paris, lxxxiv (1913), p. 357.
† Bristol Med. Chir. Jour. (June 1894).
‡ Paris Thesis (1886).
§ Zurich Thesis (1875).

As to the frequency of the different etiological factors the statistics of Weill* show that in over 5000 cases one-fifth were due to tuberculosis and four-fifths to rheumatism. In all the cases of pericarditis which this investigator was able to follow up, in children between the ages of 2 and 15 years, two-thirds went on to the formation of adhesions.

Whether syphilis may be a cause of this condition is not certain. French authors are inclined to believe that it is frequently a factor to be reckoned with. We have seen a child of seven with adherent pericardium and mitral and aortic endocarditis, with a 4+ positive Wassermann reaction; but whether the latter condition could be considered the causative factor of the cardiac condition, we are unable to state.

Pathology.—All grades of severity are met with, from a few simple strand-like adhesions running from the visceral to the parietal pericardium to conditions of complete obliteration of the pericardial cavity. Adhesions are at first thin, delicate and easily torn; but as they organize they contract and gradually unite the two surfaces of the pericardium. In advanced cases the heart is encased in a thick fibrous envelope, which may reach a thickness of 2 cm., and which is composed of the visceral and parietal layers of the pericardium and the interposed mass of newly formed connective tissue. Rarely calcareous deposits are encountered. The pericardial layers can usually be separated by traction, but in cases of very long standing, organization of the adhesions has gone on to such a degree that this is no longer possible. On cross section the new formed tissue often shows a reticulated, sponge-like structure; the interstices and cavities between the adherent bands being filled with fluid or semi-fluid material, so that the separated surfaces resemble tripe in structure. This productive inflammation may extend inward so as to involve the heart muscle, or outward to the external surface of the pericardial sac with resulting pleuropericardial adhesions and indurative mediastinitis.

In the tuberculous form, miliary tubercles may be found on the pericardium or cheesy deposits may occur among the adherent bands. This may be associated with tuberculosis of the pleura, mediastinal lymph nodes, or peritoneum. The pericarditis in such cases may be a part of a general polyserositis.

The heart itself behaves differently, according to whether the disease is rheumatic or tuberculous in origin. In the former case endocarditis is usually present and the heart is much enlarged. In fact adherent pericardium gives rise to some of the largest hearts encountered in childhood. Many theories have been advanced to explain why this great hypertrophy should take place. It has been suggested that when external pericardial adhesions are present, the traction exerted by these bands during respiratory thoracic movements may directly pull upon the heart and cause its expansion. However, very markedly enlarged hearts are seen in cases in which

**Loc. cit.*

the external pericardial adhesions are absent. Another explanation advanced is that the disease being due to repeated acute attacks, the hypertrophy is the result of the relatively strong and vigorous heart of the child attempting to throw off each recurring infection by a sudden increase in its size.

The myocardium may be involved, at times to a very marked extent, causing extreme fatty infiltration.

As the disease progresses the heart becomes less and less able to take care of the circulation, so that dilatation of its chambers results. Gradually all the pathological phenomena of broken compensation appear—congestion, edema, ascites, etc.

The rôle played by the liver in cases of adherent pericardium is especially interesting, since we here meet with the so-called "iced liver," the "Zuckergussleber" of the Germans. In this condition, described by Pick and by Hutinel and Moizard, the liver is found to be the seat of a type of cirrhosis. According to the first named author* "there is a symptom complex, pericardial pseudocirrhosis of the liver, remarkably similar to the mixed form of hepatic cirrhosis (with enlarged liver marked ascites, and no jaundice). This condition is brought about by circulatory disturbances in the liver, following pericarditis, which lead to the production of connective tissue resulting in marked portal stasis with most pronounced ascites. This symptom complex occurs especially in young individuals, but may also be observed in later life." The liver in such cases is found enlarged, with chronic congestion and fibrous hyperplasia. Its surface is covered with a thick capsule of dense fibrous tissue whence the name "iced liver." According to Rolleston,† this condition is closely allied to chronic hepatic venous engorgement and is to be distinguished from cases in which the pericarditis and perihepatitis are accompanied by chronic peritonitis and pleurisy—such cases falling into the group of multiple serositis.

Symptoms and Physical Signs.—The onset of the disease is usually insidious, numerous acute attacks having preceded it or the child having complained of fleeting joint pains, so that no attention whatever has been paid to the cardiac symptoms. Gradually it is noticed that the child is failing, is becoming progressively weaker and paler, and only then do the evidences of cardiac failure begin to appear. In other cases, especially those of the pseudocirrhotic type, ascites may be the first symptom, so that the condition may be incorrectly considered tuberculous peritonitis. Another common mode of onset, in the cases in which endocarditis is also present, is the following: After the child has been kept in bed for what was considered only an attack of endocarditis, he is allowed up but does not seem well. After several weeks of slight indisposition, careful examination reveals some of the signs of adherent pericardium, and the physician realizes that he has been dealing with an insidious form of pericardial inflammation.

* F. Pick, Zeitschr. fur Klin. Med., xxix (1896), p. 385, Nos. 5 and 6.

† Diseases of the Liver, Gall Bladder and Bile Ducts, London (1912).

When fully developed the subjective symptoms of pericardial adhesions are usually those arising from cardiac failure—dyspnea, precordial uneasiness or pain, hepatic tenderness, vomiting, edema, ascites, cough, etc. The following are the most important of the physical signs:

1. Systolic retraction of the third, fourth and fifth intercostal spaces to the left of the sternum. This phenomenon though it may occur in the absence of adhesions, when there is marked cardiac enlargement and flabby intercostal musculature, is rather characteristic.

2. Systolic retraction of the left postero-lateral thoracic wall (Broadbent's sign). To elicit this sign the child should be placed in the sitting posture in a good light and viewed from behind. If the pericardium is adherent to the structures about it, a systolic retraction will be noted in the region of the tenth and eleventh interspaces followed by a diastolic rebound which may be felt as well as seen.

3. Immobility of the apex beat when the child's posture is changed.

4. Systolic recession of the apex.

5. Immobility of the epigastrium in respiration, due to the impeded descent of the diaphragm in inspiration.

6. Sudden diastolic collapse of the veins of the neck.

7. Palpable diastolic shock over the base of the heart.

8. Paradoxical pulse.

9. Signs of cardiac enlargement.

10. Roentgen-ray examination. (See below under Diagnosis.)

Course and Termination.—As a rule, after physical signs of adherent pericardium have become evident, the disease progresses rapidly and, especially in the younger children, soon terminates fatally. The heart hypertrophies and dilates, the symptoms of decompensation become more marked, and the patient succumbs after a few months or years.

The prognosis of this disease in children is particularly bad since adhesions seem to have an especially detrimental effect on the growing heart Death may occur suddenly from syncope, or else the child may decline gradually with so-called cardiac cachexia. Occasionally an ulcerative endocarditis terminates the illness (Weill). Rarely is the course a very chronic one, and the adhesions are apparently well borne by the heart, as in the case of adults. The tuberculous variety is usually fatal within one year after its onset.

Diagnosis.—As has been mentioned above, adherent pericardium may run an entirely latent course, no diagnosis being made until the case comes to post-mortem section. The occurrence of the disease should be kept in mind in connection with all long-standing cases of endocarditis, especially those which are apparently not doing well, or those in which acute pericarditis has previously been noted. Adherent pericardium must also be suspected in children in whom unexplained ascites with edema of the legs appears. The cases in which pseudo-

cirrhosis is found must be differentiated from true hepatic cirrhosis and from tuberculous peritonitis. It is advisable also in the latter type to have a Wassermann test performed for, according to some, hereditary syphilis may be a factor (Hutinel).

The differentiation of the heart enlarged by endocarditis from that due to pericarditis is made more difficult by the frequency with which both these conditions are present at the same time. The signs of cardiac decompensation and those of endocardial involvement (murmurs) lead the examiner to overlook the signs of pericardial adhesions. In such cases the Roentgen ray may be of service.

Where the adhesions are limited to the contiguous surfaces of the pericardial sac, the fluoroscope merely reveals small fluttering pulsations and diminished respiratory mobility. On the other hand, where the adhesions involve the outer surface of the pericardium, the Roentgen ray gives very characteristic evidence. In such cases the adhesions appear as bands, projections, or notches along the cardiac outline, so that the smooth cardiac outline seen in hypertrophy or dilatation is replaced by an irregular notched uneven one. Strands may be seen running to adjacent structures, especially to the diaphragm. On deep breathing, these bands cause small tent-like shadows in those spots where the diaphragm's descent has been impeded. On lateral transillumination, such bands may be seen running through the anterior and posterior mediastinum, obliterating these usually clear spaces. The normal angles formed by the heart with the diaphragm may be obliterated, the adhesions forming dense shadows. The immobility of the heart on change of position is well shown. In cases of very marked mediastino-pericarditis, the heart silhouette may be entirely lost in the dense irregularly shaped shadow cast by the masses of fibrous adhesions.*

Treatment.—The therapy of adherent pericarditis is very unsatisfactory It includes the treatment of the cardiac decompensation. The underlying causes such as rheumatism, tuberculosis or syphilis require their respective treatment. In long-standing cases iodides are of use. Fibrolysin is recommended but apparently does little good. In cases in which ascites is prominent, repeated abdominal paracentesis is often necessary. The operation of cardiolysis, first advocated by Brauer, may be resorted to in cases of great severity, a number of such operations having been reported in children who had been greatly benefitted.

MYOCARDITIS

Myocarditis in childhood is chiefly of importance because it is an accompaniment of every case of cardiac inflammation, and because it is mainly upon the condition of the heart muscle that the outcome of any serious cardiac disease depends. It must, however, be understood that uncomplicated myocarditis, especially the chronic form, is very rare during childhood.

* Dietlen, *loc. cit.*

The heart muscle is subject to two distinct types of inflammation:

1. Parenchymatous degeneration of the heart muscle is the result of the action of bacteria or toxin in acute infectious diseases, such as scarlet fever, diphtheria or pneumonia. The heart muscle assumes a pale grayish color. It loses its tone and becomes friable and flabby. Small yellow streaks due to the deposition of fat, and red areas due to minute hemorrhages appear. Microscopically the muscle fibers show cloudy swelling, the transverse striations disappear, and fat droplets are deposited. In severe lesions there is hyalin degeneration of the fibers and in very acute cases, areas of inflammatory reaction may be found, with leukocytic infiltration, edema and deposits of fibrin. Rarely abscess formation results.

FIG. 119.—Section of left ventricle from a case of acute rheumatic carditis. Submiliary nodule or "Aschoff body" (*A*); endocardium (*E*); myocardium (*M*).

Aschoff has described a special form of cardiac infiltration occurring in acute rheumatism, in the form of microscopic foci, forming submiliary nodules. These structures, now known as Aschoff bodies, consist of aggregations of large cells scattered throughout the myocardium, mainly in the subendothelial portion, in the course of the medium sized and the smaller blood vessels. The cells, according to their discoverer, are of connective tissue origin, and with them are mingled lymphocytes and eosinophilic leukocytes. The nodules are most commonly found in the musculature of the posterior wall of the left ventricle. These lesions are considered pathognomonic of acute rheumatic infection.

Figure 119 shows a typical Aschoff body, from a case of fulminating carditis with erythema multiforme following tonsillitis, in a child aged three years, dead 18 days after the onset of the illness.*

* Bass, Medical Clinics of North America (July, 1918).

2. Interstitial myocarditis is much less common. There may be infiltration with round cells in foci or scattered between the muscle fibers. If recovery takes place, scar formation results.

Syphilis may cause either parenchymatous or interstitial myocarditis. Adler* reported that the hearts of syphilitic infants might show typical proliferating endarteritis. More recently, Warthin† has found the spirocheta pallida in a large number of hearts of children infected with syphilis. In fact the spirochetes may be found in the heart when they can be demonstrated nowhere else in the body. The organisms may be present without causing any demonstrable lesion. On the other hand, marked tissue changes may occur, and purely parenchymatous lesions may be found, especially in virulent congenital syphilis. Warthin is of the opinion that syphilis is a very important factor in the causation of heart lesions, both myocardial and endocardial.

Myocardial degeneration may, in rare instances, lead to acute cardiac aneurisms and even to rupture of the heart. These results follow severe acute inflammation, such as occurs in pyemia or septic scarlet fever; or they may follow chronic interstitial inflammation, as in the case of a five year old child with congenital syphilis, reported by Anderson.‡

The symptomatology of myocardial inflammation is vague. As the heart muscle becomes involved the heart sounds change in character. The first sound at the apex becomes dull and loses its muscular quality. Dilatation may occur, and with it a soft blowing murmur appears over the apex due to relative mitral insufficiency. The heart beats more rapidly, but the pulse is weaker and less full. Irregularity of the pulse and abnormal rhythms, such as gallop rhythm or embryocardia, make their appearance.

Acute myocarditis is seen by the pediatrist probably most often in the course of diphtheria. Here the first indication of the toxic action on the heart may be sudden marked pallor together with a weak, rapid, and irregular pulse. Vomiting and epigastric pain are common. Marked restlessness and dyspnea appear. The pulse becomes more and more irregular, and any of the abnormal rhythms such as premature beats, heart-block or auricular fibrillation may be established. Attacks of syncope are frequent, and sudden death may take place. These symptoms come on late in the disease after all local signs of diphtheria have disappeared (Fig. 120).

Mention must also be made here of vagus paralysis, which may occur either very early in diphtheria in the septic cases, or later on, especially in the cases which also show other post-diphtheritic paralyses and nephritis. The clinical picture here is one of very rapid cardiac failure, with marked engorgement of the liver, vomiting, clammy cold

* N. Y. Med. Jour. (1898), p. 577.

† Seventeenth Internat. Congr. Med., Sec. Gen. Path. and Path. Anat., Part II; Am. Jour. Med. Sc., cxli (1911), p. 398.

‡ Lancet (Mar. 27, 1915).

extremities, cyanosis, dyspnea, marked restlessness, mental apathy and slight confusion. The child's condition rapidly becomes worse, and death takes place in coma or in convulsions.

The prognosis of acute myocardial inflammation as a rule is not good. A large percentage of the children succumb. There is great difficulty in making the diagnosis, since so many of the symptoms may be present in any acute infectious disease merely as the result of the fever. We may diagnose myocarditis when the circulatory symptoms are out of proportion to the general symptoms of intoxi-

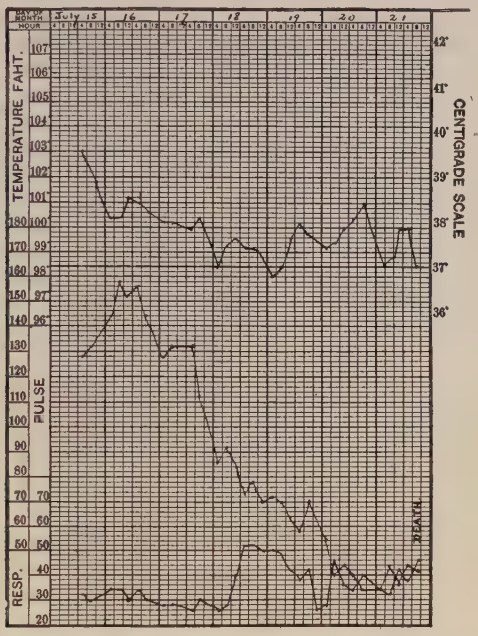

FIG. 120.—Acute myocardial degeneration in diphtheria. (Girl aged five years. Death on the seventh day of illness.) Note the extremely rapid fall in the pulse rate. On the sixth day of illness the pulse rate is 34 while the respirations are 40 per minute. (From the service of Dr. Eli Long at the Willard Parker Hospital.)

cation, and when definite signs of severe heart involvement are present (persistent arrhythmia, dilatation, etc.). Simple tachycardia or the presence of blowing systolic murmurs over the heart are not enough upon which to base a diagnosis.

We have seen several cases in infants in whom a sudden even if temporary drop in the pulse rate during an infectious disease was of sinister significance. Figure 121 is an example of such a case. The history is briefly as follows:

Harry T., aged 17 months, was well up to his sixteenth month, when he developed measles, followed by enteritis, nephritis, and one week later by pneumonia. On the fifth day of the pneumonia the temperature fell to 97° and the pulse, which during the preceding

days had varied between 136 and 180, dropped to 88 where it remained for about 12 hours. After this the pulse and temperature again rose, and then during the course of the next week, gradually came down again, the temperature remaining about normal and the pulse rate varying from 126 to 140. On the fourteenth day of the illness the infant was apparently much improved. At 11:30 o'clock it was sitting up in bed taking its feeding well. At 12 o'clock the child became suddenly cyanosed, the pulse became very feeble, then imperceptible, and in one-half hour, in spite of the most vigorous stimulation, the child was dead. The autopsy revealed only a myocarditis.

The treatment of myocarditis consists chiefly in absolutely sparing the heart by enforcing complete rest, both mental and physical.

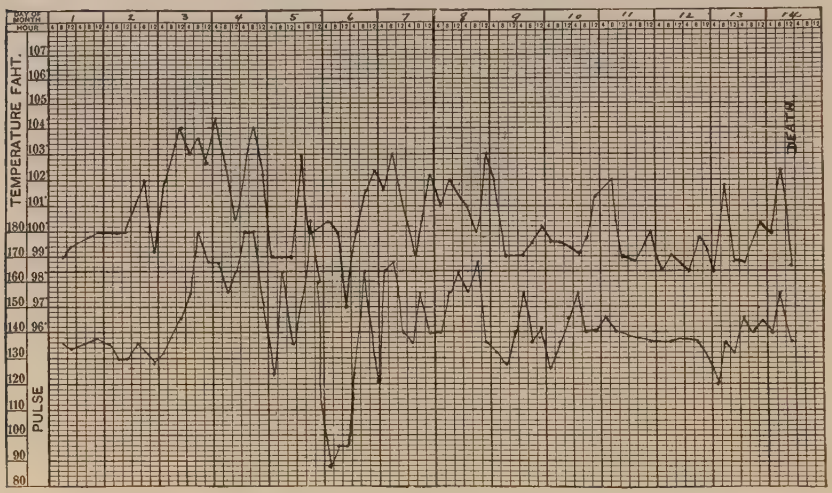

Fig. 121.—Chart of temperature and pulse rate in pneumonia complicated by myocarditis. Note the abrupt drop in the pulse rate on the fifth day. Sudden death on the fourteenth day.

Ice bags may be applied to the precordium. For the attacks of syncope, caffein, camphor or adrenalin are useful. Heat should be applied to the extremities. For the restlessness and marked tachycardia small doses of morphin and codein are advisable. If the child survives, rest treatment must be persisted in for a long time; if symptoms of dilatation supervene, digitalis therapy is indicated.

FATTY DEGENERATION OF THE HEART

Fatty degeneration of the heart is met with in severe infections, especially in diphtheria, where the process may be extremely marked. It is also seen in cases of phosphorus poisoning, severe burns, and after profuse hemorrhages as in the course of purpura. Profound anemia, such as occurs in leukemia, may also give rise to fatty changes in the heart. Occasionally it is found in connection with rheumatic

carditis, as in the case of chorea described by E. Weill and Gallavardin.* The symptoms are those of myocardial insufficiency.

The heart may also be involved in cases of general fatty degeneration in the newborn (Buhl's disease) and in the cases of septic icterus, cyanosis and hemoglobinuria grouped together under the name of Winkel's disease.

ENDOCARDITIS

No disease occurring during childhood deserves more careful attention than inflammation of the lining membrane of the heart. This condition is of importance not only because of its relative frequency but chiefly because, involving as it does so important an organ as the heart, its outcome and especially its sequelæ are of the utmost consequence to the child's future welfare.

Classification.—Cases of endocarditis may be classified into various groups depending upon whether the symptoms, the etiology, or the pathology is used as a basis of classification. From the symptomatic side we speak of acute, subacute and chronic, or of benign and malignant cases. Pathologically, the cases may be divided into verrucose which correspond to the benign, and ulcerative which correspond to the malignant. From the etiological standpoint we may divide the cases according to the causative agent and thus speak of rheumatic, pneumococcic, gonococcic, etc., varieties.

In childhood the vast majority of cases of endocarditis are acute in character. True chronic inflammation of the lining of the heart and its valves, such as occurs in adult life in the course of arteriosclerosis or Bright's disease, is very rarely found, and it is obviously incorrect to speak of chronic valvular disease under the head of chronic endocarditis. It must be understood that the crippled and shrunken valves are the result of the damage done by an acute inflammatory process, and that the progressive increase in any valvular lesion is due either to the continuation of the acute inflammation, to recurrent attacks of acute disease, or to the shrinking and fibrosis occurring as part of the process of repair. Occasionally a truly chronic inflammation may occur, as in syphilitic disease or, according to the French school (Teissier and Potain), in the course of tuberculosis.

Etiology.—Acute endocarditis is rarely, if ever, a primary disease. In the vast majority of cases it is secondary to rheumatism. Indeed so large a percentage of the cases are due to this cause that some authors deny the existence of primary endocarditis, claiming that the rheumatic manifestations have been overlooked. On this point we may quote Still: "Perhaps it would be rash to say that rheumatism is the only cause of endocarditis in childhood, but my own experience strongly suggests this. Out of 150 cases in which I have investigated this point, 142 showed evidence of rheumatism, either in articular rheumatism, subcutaneous nodules or chorea."†

* Arch. de Med. des Enfants (Apr., 1900).

† Common Disorders and Diseases of Childhood, London (1912), p. 456.

Rheumatism is given by von Dusch as the etiological factor in 22 out of 30 cases. In a series of 258 cases of endocarditis collected by Weill, 189 are ascribed to rheumatism and chorea. Church* found 80 per cent. of his endocarditis cases attributable to rheumatism, and Holt obtained the same percentage in a series of 117 cases.

In view of these figures, it is evident that acute endocarditis is very closely associated with rheumatism in early life. In fact, we should look upon acute inflammation of the heart valves rather as one of the manifestations of rheumatism in childhood than as a complication of that disease.

The prevailing belief that chorea is a rheumatic manifestation strengthens the above assertion, for endocarditis and chorea are very frequently encountered in the same individual. Thirty per cent. of cases of endocarditis collected by Holt showed evidence of chorea at some period of their disease. Weill records chorea as the cause of endocarditis in 15 per cent. of his cases; Hochsinger, who finds the same percentage, declares that one-half the cases of chorea which have come under his observation suffered at some time from endocarditis. Autopsies performed in fatal cases of chorea reveal endocarditis in a very large percentage of cases (Pye Smith, 11 times in 11 cases; Ogle, 10 out of 16 cases; Stephen Mackenzie, 2 out of 2 cases; Dickinson, 3 out of 10 cases) (quoted by Weill).

The age incidence of rheumatism and acute endocarditis also points strongly to their close relationship.

The connection between acute inflammation of the tonsil and disease of the heart is of very great importance. It frequently happens that an attack of acute tonsillitis is directly followed by endocarditis. The removal of diseased tonsils, therefore, becomes a very vital part of the prophylaxis of heart disease. As a rule, the operation of tonsillectomy is followed by no evil influences on the heart, but exceptions to this may occur, for occasionally a heart previously sound becomes infected directly after tonsillectomy, evidently as a result of the operative procedure itself. Such postoperative heart involvement may proceed as a mild low-grade infection, in which slight cardiac enlargement and the development of a murmur are the only evidence of local cardiac trouble, or else very severe septic endocarditis with fatal outcome may result. Either type of infection, however, occurs so rarely that one should not take this contingency into consideration when deciding upon operation in cases where there are distinct indications for surgical interference.†

Contrary to the generally accepted view, scarlet fever is not a frequent cause of endocarditis. Some authors (Pospischill) go so far as to deny absolutely the existence of a scarlatinal endocarditis, but this attitude is undoubtedly too radical. Both a benign variety, similar to that seen in rheumatism, and a malignant one are occasionally met with. That the virus of scarlet fever has not a very decided

* Quoted by Hochsinger.

† Koplik, Am. Jour. Med. Sc., cxliv (1912), p. 30.

tendency to attack the heart valves is shown by statistics. In a large scarlet fever service we have not seen the development of any case of endocarditis. Moreover, we have had occasion to observe a number of children with rheumatic endocarditis pass through severe scarlet fever without any apparent change in the endocardial condition. This subject is made all the more obscure by the fact that in cases of scarlet fever we meet with joint symptoms, the so-called "scarlatinal rheumatism," which may in truth be nothing less than intercurrent attacks of true rheumatism. Endocarditis occurring in such cases might therefore very properly be ascribed to the rheumatic rather than the scarlatinal factor in the illness. This is the stand taken by Still. However, cases such as are reported by Clements* or by Schick† would seem to be sufficient proof of the existence of scarlatinal endocarditis as a clinical entity. The latter author reports the case of a girl aged six years who, after a mild attack of scarlet fever, developed temperature, palpitation, and tachycardia. This was followed by gradual enlargement of the heart and the development of a systolic apical murmur, transmitted to the axilla, becoming permanent. In other words, we have here the production of a typical case of mitral insufficiency.

Severe, malignant types of endocardial inflammation are met with in the course of scarlet fever, more as a part of a general sepsis than as part of the disease itself. Thus, phlegmonous neck inflammations may give rise to general septic infection with localization of the process on the valves of the heart. Such are the cases which occur in combination with purulent pericarditis.

According to French observers, tuberculosis is a frequent cause of endocarditis. Thus, Weill goes so far as to place this disease next to rheumatism and chorea as the most frequent etiologic factor, finding it 15 times in 279 cases, *i.e.*, a percentage of 5.7. Cases are described in which the valves are the seat of tubercles in the course of general miliary tuberculosis; or else larger caseating foci involving the heart wall may be present (Letulle, Tripier). Neither American, English, nor German authors lay great stress upon tuberculosis as a cause of endocarditis, and it seems probable that in childhood it should be classed as a rare cause of the disease.

Other diseases to which endocarditis is said to be secondary are measles, pneumonia, variola, diphtheria, typhoid, relapsing fever, and influenza. A careful critique of the case reports, however, in many of the above mentioned diseases leads us to great skepticism in accepting them as etiological factors.

The gonococcus, a not infrequent cause in adult life, may also, in rare instances, set up inflammation of the heart valves in children.

As to the variety of organism which invades the heart valve, it has been shown that the streptococcus, staphylococcus, pneumococcus, and gonococcus are by far the most important. The influenza bacillus

* Lancet, ii (1909), p. 1140.

† "Scharlach," Escherich and Schick, Vienna (1912).

and in single cases, various other organisms are reported, but such organisms as the Bacillus typhosus, diphtheriæ, or coli are probably not the actual cause of the lesions, but may play the part of secondary invaders (MacCallum).

Age Incidence.—Acute endocarditis occurs during fetal life, as a rule, on the right side of the heart and in conjunction with developmental defects. Of the post-natal infections, one of the youngest cases is that reported by Czerny in an infant of one month suffering from septic endocarditis. Such a case, however, is very exceptional since endocardial inflammation is rare in children under two years of age. In 1000 post-mortem examinations, Holt found no case of acute endocarditis in children under three years of age. Steffen (quoted by Lempp), in tabulating 45 cases of endocarditis in children, found 5 in children under one year. von Dusch, in the same number of cases, reports 5 in children between the ages of eight months and five years. Lempp* reports seven definite cases from Finkelstein's clinic. All of these are in infants, and the mitral valve was shown by autopsy to have been involved in every case. Finkelstein† reports 15 cases of endocarditis in infants, and believes that even at this early age, two-thirds of the cases are due to rheumatism, the other third being a manifestation of sepsis.

After the second year, and thereafter as the age of the child increases, endocarditis becomes more frequent, as is shown in the following table taken from Sansom:

Age, years	1	2–3	4	5	6	7	8	9	10	11	12
Number of cases	2	5	7	8	15	14	11	17	18	23	9

Of 53 cases observed by Hochsinger, 12 were under 5 years and 41 between 5 and 12 years. In 109 cases of rheumatic endocarditis collected by Weill, 10 were below 8 years, and 99 were between 8 and 15 years.

From these figures it is evident that as far as age is concerned, the following statements hold true: Endocarditis may rarely occur in the fetus. It is very rare under two years of age, but undoubted cases have been described in infants as early as the first month. It increases in frequency as the age of the child increases, being especially prevalent about the age of puberty.

Females are apparently slightly more susceptible than males.

Pathology.—As in adult life, two forms of endocarditis may be distinguished—verrucose and ulcerative—though it must be understood that both are merely more or less advanced stages of the same process.

1. Verrucose Endocarditis.—The lesion consists of wart-like excrescences which occur, as a rule, on opposing surfaces of the valves,

* Monatschr. f. Kinderh., vi (1907), p. 78.

† Lehrb. d. Sauglingskrankheiten.

at the line of closure near their free margins. Only the surface of the valve exposed to the blood stream is involved. Tiny translucent bead-like excrescences develop on the valves. Microscopically, these vegetations are found to consist mainly of fibrin with few cells. Microörganisms may or may not be demonstrable. At one time it was held that the vegetations of true verrucose endocarditis, the result of rheumatism, contained no bacteria. This view has, however, been generally abandoned, and rheumatic endocarditis is looked upon as probably a bacterial disease. In the majority of cases, this type of endocarditis subsides and the tissue of the vegetations organizes, leaving a scar in the valve.

2. Ulcerative Endocarditis.—In this condition the vegetations are large and succulent. They proliferate rapidly and destroy the valve substance as they grow. They involve not only the valves, but spread either by direct contact or by progressive involvement to the adjacent mural endocardium. The valve mechanism is disturbed by the intrusion of the vegetations between the cusps. Ulcerative and destructive processes spread along the chordæ tendineæ to the papillary muscles and the heart substance itself. Microörganisms are always present in the lesions.

Septic emboli are common, for pieces of the friable vegetations are easily broken off, and are carried by the blood stream to distant organs where new infectious foci arise (spleen, kidney, lungs, brain, etc.).

In acute endocarditis the heart muscle is always involved and the pericardium very frequently. Attention was first called to this point by Sturges in 1895,* who proposed the term "carditis," having shown by post-mortem material that in the majority of acute inflammatory conditions involving the heart, and especially in rheumatism, all the layers of that organ are involved. Thus in 83 cases of heart inflammation in children examined at autopsy, 7 showed endocarditis without pericarditis; 28 pericarditis without endocarditis, while 48 showed endocarditis and pericarditis, i.e., carditis.

In diagnosing endocarditis at autopsy, great care must be taken, especially in very young children, not to mistake for vegetations the so-called Albini's nodes. These are pin-head sized, spherical structures which are found near the free edges of the valves, usually the auriculoventricular and more rarely the semilunar. They are capillary dilatations or small blood cysts covered with endothelium. They are of no clinical significance whatever and are of importance only because they are so easily mistaken for evidence of endocardial inflammation.

Symptoms.—Simple Endocarditis.—The onset of simple endocarditis is as a rule insidious; even the primary cause, such as mild rheumatic manifestations, may be entirely overlooked. Such are the cases in which valvular disease is first discovered during the routine physical examination of school children. Probably the majority of cardiac cases seen in dispensary practice in the larger cities are those

* Lumleian Lecture, "Heart Inflammation in Children," London (1895).

referred to the clinic by the school physician. The parents of such children are often quite unable to recall any definite illness which might be considered as the starting point of the cardiac infection. Children with such mild inflammation present no subjective symptoms, and as long as no reinfection takes place, and as long as the heart remains compensated, appear perfectly well to the casual observer.

The most important single symptom of acute endocarditis is fever. Pyrexia of all grades and types may be met with. Since the endocarditis is usually secondary, we may find the temperature of the original disease modified by that of the new complication. Thus in a case of acute tonsillitis, instead of disappearance of the fever in the course of a few days, we note a continuance of the temperature, although the local signs in the throat have disappeared. Such persistent fever in any infection, especially one in which endocarditis occurs, should at once draw attention to the heart.

There is no typical variety of fever. The temperature chart may resemble that of malaria; it may remain continuously above normal; or very marked remissions may occur. We have had under observation a case of rheumatic endocarditis in a 10 year old child in whom an exacerbation of the disease was accompanied by daily rises to 102 or 103 degrees and remissions to 97 degrees every evening for several weeks. Afebrile cases are rarely encountered in which valvular lesions may develop in a child under continuous observation where the temperature never rises above 98.6 degrees (von Jurgensen, "Endocarditis" in Nothnagel's System).

Pallor is an important symptom. The history of increasing pallor, especially if coupled with breathlessness on exertion, and a tendency to become very easily fatigued, should draw attention to the heart. The following is an example of such a case:

John X., aged seven years, is brought to the physician because of anorexia and pallor. The boy has never had any illness excepting measles at the age of four. On close questioning, the mother recalls that two weeks previously the boy had complained of pain in the right hip-joint, which she had attributed to a strain sustained while turning somersaults.

Physical examination revealed a pale, tired looking boy. Temperature 101 degrees. Pulse 130 at rest. Heart: Apex beat in the fifth space one finger's breadth outside the nipple. Percussion shows the left border beyond the nipple. At the apex the first sound is accompanied by a soft blowing systolic murmur transmitted outward. Second pulmonic sound extremely loud and snapping in character. Pulse small and rapid. Spleen just palpable.

Subsequent course: After several weeks in bed, the heart dulness decreased, the pulse rate and temperature became normal; the systolic murmur, however, persisted.

Failure to gain in weight, headache and epistaxis are suggestive symptoms.

It will be noted that we have so far made no mention of symptoms directly referable to the heart, for in children these are conspicuously infrequent. Palpitation, precordial pain and distress are much more often found in cases of functional cardiac disease than during acute involvement of the endocardium.

Rapidity of the pulse is of considerable importance. It is a safe rule to follow that if tachycardia is present after the acute symptoms of a rheumatic attack (tonsillitis, arthritis, chorea, etc.) have subsided, the child's heart should be very carefully watched, for it is in such cases that one finds murmurs developing later on.

The physical signs at the heart are as follows: Inspection shows cardiac pulsation over a wider area than normally. The impulse may be visible in the area beyond the nipple line, and instead of the normal movement may show a forcible and exaggerated pulsation. Considerable stress is laid by some (Osler) on inspection of the precordium, since in children the thin chest walls enable one to observe the heart movements more accurately than in adults. Palpation also aids in locating the impulse. Thrill is not common. Exaggerated snapping closure of the pulmonic valves may often be felt, and is at times the first indication of serious endocardial damage. Percussion will reveal the outward extension of the cardiac dulness. In very young children accurate mapping of the precordial dulness is a matter of extreme difficulty, and we have found by control with Roentgen rays, that even in older children, percussion of the heart borders may lead to very incorrect deductions. However, when definitely demonstrable, enlargement of the cardiac dulness is of considerable importance, for probably every case of endocarditis is accompanied by more or less involvement of the myocardium, leading to slight dilatation.

Auscultation may reveal the first evidence of beginning endocarditis. A muffling of the first heart sound at the apex may be the first sign to appear. As the valve becomes more involved this sound is gradually replaced by a soft blowing systolic murmur. At the same time the second sound over the pulmonic area becomes accentuated. As the disease progresses, the character of the murmur may change, the blowing quality being replaced by a harsher one. The above described signs refer to cases in which the mitral valve alone is involved. These constitute the great majority. The aortic valve, however, is very rarely affected, though such instances when they do occur are almost invariably coincidental with disturbances of the mitral valve. The spread of the inflammation to the aortic valve is accompanied by the appearance of a soft systolic murmur heard loudest over the second right interspace close to the sternum. Later on, when the size of the vegetations or the resulting valvular shrinking cause a leak at the aortic orifice, the characteristic diastolic murmur appears.

Course and Prognosis.—Acute endocarditis may go on to complete recovery, or else, as in the majority of cases, a gradual disappearance of the acute symptoms gives place to the picture of chronic

valvular disease. In cases which go on to recovery, the temperature becomes normal, the pulse rate decreases, and the murmur, which may have been definitely present for many days (55 days, Steffen), disappears, leaving an apparently healthy heart. When the aortic valve is affected, complete restitution never takes place.

Serious complications often appear. The most important are pericarditis and myocarditis. Embolism in simple acute endocarditis in childhood is rare. Cases of hemiplegia, even in young children, have, however, been described.

The picture of acute endocarditis as it appears in infants, is quite different from the disease in older children. It is to Finkelstein that we are indebted for a clear description of this clinical picture. This observer lays great stress on the fact that in very young babies the symptoms of endocardial inflammation are mainly respiratory in character. Occasionally, even in infants, a case is met with in which the typical symptoms as they occur in older children are found. Such cases present fever of an irregular type, prostration, signs of cardiac weakness which may be accompanied by murmurs, and dilatation of the heart. Such cases have been described with joint swellings and purpuric eruptions. However, typically rheumatic pictures such as this are the exception. Most often endocarditis in infancy proceeds under the guise of a general infection with no signs referable to the heart itself. In such cases one may diagnose endocarditis when in an infant with continuous fever the following symptoms make their appearance: (1) Unusual pallor bordering on cyanosis; (2) deep and rapid respirations not dependent upon affection of the lung; (3) repeated attacks of marked cyanosis. Such cases usually run a fatal course in from one to four weeks; but even infants have been known to recover from this acute disease to go on to develop permanent valvular defects.

In general, it may be said that in infancy acute endocarditis is usually fatal. In older children, on the other hand, recovery is the rule, although in the great majority of cases the heart remains permanently damaged.

Diagnosis.—When endocarditis occurs in the course of an acute illness, the diagnosis is, as a rule, not difficult. The most commonly made error is to mistake the systolic murmur which occurs in febrile conditions, probably as the result of cardiac dilatation, for the murmur of endocarditis. This is a very frequent mistake in the course of chorea, where myocardial involvement and anemia may give rise to systolic apical murmurs. In such cases one may be guided by the following points: The murmur due to true inflammation of the heart valve is constant. It is present regardless of the child's posture. It is usually best heard at the apex and is transmitted toward the axilla. It may have been preceded by impurity of the first sound. This last point is considered by some French authors as the most important, for they believe the impurity of the first sound to be a better criterion of the presence of endocarditis than the murmur itself.

The presence of a loud pericardial murmur often obscures the auscultatory signs of a coexisting endocarditis.

Of considerable importance is close observation of the size of the cardiac dulness, as its increase may be the first sign of a valvulitis.

Of the general symptoms, tachycardia, breathlessness, pallor, languor and epistaxis should draw the examiner's attention to the heart.

Treatment of acute endocarditis is considered in the chapter on Chronic Valvular Disease.

Malignant Endocarditis.—In reference to the simple variety, infective endocarditis must be looked upon as a more virulent kind and a more advanced stage of endocardial inflammation. The heart may be the primary seat of the disease or it may simply become one of the foci in a septic process originating in any part of the body. The latter type of case is not difficult to recognize, but it is only with the advent of more perfect methods for the detection of living organisms in the blood stream that we have been able to diagnose those cases in which the heart is apparently the primary focus of the disease.

It is also due to the perfection of bacteriological technique that infective or bacterial endocarditis has been shown not to be the very rare disease it was once considered.* Writing in 1900, S. S. Adams (Jacobi Festschrift) was able to collect from the literature only 46 cases of infective endocarditis in children. Since, however, it is becoming customary to examine the blood culturally in cases of endocarditis with fever, as well as in those where the fever is of obscure origin, more cases of this disease are being brought to light. Thus Horder† reports a series of 150 cases of the disease of which 16 are in individuals under the age of 15 years—in other words, 10 per cent. of cases of bacterial endocarditis occur in childhood.

The disease becomes more common as the age of the individual increases. Cases have been reported, however, occurring in earliest infancy. Bidone's case (quoted by Adams) was in a newborn infant which lived only 19 hours, and in whose blood streptococci were found—the mother suffering from erysipelas at the time of labor. Other cases at eight months and a year are described. In Horder's series there were two cases under 5 years of age, five cases between 5 and 10 years, and nine between 10 and 15 years of age. The sexes are equally affected.

The organisms causing the disease are various, the most common being the streptococcus. Other bacteria which have been recovered in this disease in children are the staphylococcus, pneumococcus,‡ gonococcus,§ influenza,‖ pyocyaneus.¶

* Critical Review, I. Simons, Quart. Jour. Med. (Apr., 1914).
† Quart. Jour. Med., ii (1908–1909).
‡ Dean, Proc. Royal Soc. Med., v (1912).
§ Marfan and Debre, Soc. Med. Hôp., Paris, xxix (1910).
‖ Horder, *loc. cit.*
¶ Blum, Centralbl. f. Bakt., xxv (1899).

Infective endocarditis may appear under very different guises depending upon the primary disease, the resistance of the child, and especially on the virulence of the infecting organism. These factors result in the disease pursuing an acute, a subacute, or even a chronic course. The two last named are included under the term Endocarditis Lenta, in which an attenuated form of the streptococcus is recovered from the blood. The duration of such cases may be prolonged, Horder describing one of five month's duration in a boy aged 12 years.

Already existing valvular defects and congenital deformities of the heart predispose to this infection. We may therefore find children, sufferers from rheumatic heart disease, who begin to run a septic temperature and gradually show all the signs of bacterial endocarditis. Such are the cases one sees referred to as malignant rheumatism, though we are as yet ignorant as to whether the infecting agent is the same streptococcus which caused the original rheumatic heart involvement, or whether it is a secondary invader.

The clinical picture of infective endocarditis is complex. Acute cases set in abruptly often with a chill and fever. Symptoms of marked intoxication and prostration appear. The joints may be swollen and painful. In some of the more fulminating cases, no symptoms referable to the heart have a chance to manifest themselves before death occurs. In others, murmurs and cardiac dilatation rapidly develop.

In the subacute cases, the onset is, as a rule, very insidious with moderate temperature, slight cough, emaciation and pallor—a low-grade sepsis. The fever may be of any type, remittent, intermittent, high or low. Gradually attention is drawn to the heart by physical signs—a faint systolic murmur may make its appearance; or more frequently when the disease is appearing in a child already the subject of valvular defect, some new murmur or some change in the old murmur draws the examiner's attention to the circulatory system. Frequent chills may occur. Emboli are common and characteristic. The spleen is enlarged, and if the site of an embolus, is tender and painful. Hematuria is frequent and is evidence of emboli in the kidney. Embolism in the central nervous system may give rise to various forms of paralytic phenomena. Petechial hemorrhages appear, often in showers, and are very characteristic. They are usually small, about the size of a pin-head, deep red in color with a tiny white central dot. They may be found anywhere on the skin or mucous membranes, and show especially well on the palpebral conjunctivæ. The color of the child changes to a peculiar café-au-lait tint (Libman). The bones, especially the sternum, become tender to pressure. Tender nodes may develop on the terminal phalanges of the fingers and toes. The blood reveals anemia and leukocytosis, and on culture shows bacteria, usually the streptococcus viridans.

The outcome in most cases is fatal.

The diagnosis rests upon three findings (Horder): (*a*) the presence of valvular disease; (*b*) the occurrence of embolism; (*c*) the demonstration of bacteria in the blood.*

The treatment of bacterial endocarditis is discussed in the chapter on Chronic Valvular Disease.

CHRONIC VALVULAR DISEASE

Etiology and Frequency.—Chronic valvular disease is in childhood, almost without exception, the result of previous acute inflammation. Its etiological factors are therefore the same as those enumerated as the cause of acute endocarditis, and we again recognize in this group the enormous importance of acute rheumatism. We may, however, even in childhood meet with a slowly developing sclerotic process in the heart valves, not preceded by an acute inflammation and proceeding as a chronic disease from its very onset. Such cases are rare and are ascribed by some to syphilis, by others to tuberculosis. Under this heading come the cases of "Pure Mitral Stenosis" (*q.v.*) supposedly due to the influence of tuberculo-toxin on the growing heart. A familial tendency to chronic heart disease has also been emphasized (Weill), several members of the same family being affected.

Statistics as to the frequency of valvular disease vary very widely according to the social status and the nationality of the children.

* A word as to the value of blood cultures in the diagnosis may here not be amiss. In recent years, the work of Lenhartz, Libman, Schottmueller, and others, has shown that living organisms may be found in the circulating blood of certain cases of endocarditis. Such may best be spoken of as cases of "bacterial endocarditis." They may or may not be "septic" in the sense that their causative organisms are pus formers; they may or may not be "ulcerative," for in some (the acute cases) there is marked endocardial ulceration, while in others, the lesions are purely proliferative; they may or may not be "malignant" in the sense that they are fatal, for we have post-mortem proof of definitely healed cases.

At the present time, therefore, we can only say that in certain cases of endocarditis, bacteria may be demonstrated in the blood during life.

The refinement of bacteriological technique has moreover enabled us to separate from this group of "bacterial endocarditis" cases certain ones presenting more or less definite symptoms depending upon the character of the organisms recovered from the blood. This is particularly true of those cases in which a non-hemolytic streptococcus, streptococcus viridans or mitis, is recovered. This organism is a small, short chained, non-encapsulated, Gram-positive coccus. On blood agar plates colonies develop in 48 to 60 hours, as fine points surrounded by delicate green rings. In glucose blood agar the colonies show precipitation on the second to the fourth day.

This organism is the common finding in the large group of subacute bacterial endocarditis cases, which are of importance because they baffle diagnosis by their protean symptoms. This so-called "endocarditis lenta" may masquerade for months as typhoid, tuberculosis, malaria or many other febrile conditions. A blood culture in such cases, if positive, absolutely clinches the diagnosis.

It is best to take a blood culture when the temperature is at its height, since it has been shown that the chance of obtaining growth is more favorable at such a time. Moreover, a single negative blood culture must not exclude the diagnosis of bacterial endocarditis, for frequently a number of cultures are necessary before a positive result is obtained.

Among 478 sick children between the ages of 2 and 15 years, Weill found 25 valvular lesions—a proportion of over 5 per cent. German authors, however, find a much lower percentage—Hauner, among 23,349 sick children of all ages, found 14 valvular lesions, 0.6 per cent.; von Dusch among 52,281, found 87, 0.17 per cent. These discrepancies are probably due to the ages of the children included in the statistics, for as we saw in considering acute endocarditis, the heart is rarely involved before the fifth year of life.

Among 1000 consecutive dispensary cases in New York City, between the ages of 2 and 15 years, the writer found 18 cases of valvular disease, an incidence of 1.8 per cent. Ten of these were girls, eight were boys.

The age incidence increases from early childhood onward as is shown in the following table from Poynton and Payne.*

150 Fatal Cases of Rheumatic Heart Disease
(Poynton and Payne)

Age, years	Number of cases	Percentage
0 – 3½	1	0.6
3½– 4½	6	3.9
4½– 5	11	7.4
5 – 6	14	9.4
6 – 7	19	12.7
7 – 8	19	12.7
8 – 9	23	15.3
9 –10	30	20.0
10 –11	18	12.0
11 –12	9	6.0

Pathology.—The site of election of valvular disease in children is the mitral valve. Among our 18 cases, the mitral was involved in 17, the aortic in 1. In a large series of cases collected by MacDonald† of 49 cases of endocarditis in children under 10 years of age, 47 were mitral cases and only 2 were aortic. These figures correspond to the German statistics of Hochsinger and Steffens who report 1 aortic to every 18 mitral cases.

Poynton and Payne give some interesting statistics concerning post-mortem examinations of 150 children dying from rheumatic heart disease. The mitral valve was affected in 149 cases. In 98, it was involved alone. Thickening of the valve was common, but a true stenosis was rare earlier than the twelfth year. The aortic valve was affected in 34 per cent., the tricuspid in 24 per cent., the pulmonic in 4 per cent. of the cases.

* Researches on Rheumatism, London (1913), p. 35.
† Glasgow Med. Jour. (1914), p. 12.

The pathology of valve defects in children differs little from that in adults. The affected valves are hardened, thickened and opaque. They shorten and their edges may fuse. Imperfect closure results, with or without narrowing of the orifice. The consequently abnormal blood flow occasions hypertrophy of the walls and dilatation of the heart chambers, with signs of stasis throughout the body as the circulation fails. Recurrent attacks of acute endocarditis are responsible for fresh vegetations which arise upon the deformed valves and further cripple them. Coincident with the endocardial disease, there is involvement of the heart muscle and the pericardium, the former giving rise to many symptoms, the latter often hastening the fatal outcome.

Symptomatology and Diagnosis.—In general, the symptoms and signs of valvular disease in children differ but slightly from those of the same disease in adults. The main differences are first, the infrequent occurrence and the relative importance of subjective symptoms, and second, the greater power shown by the child's heart in maintaining the circulation.

It is absolutely necessary to examine the heart of every sick child with care, since about one-half of the cases of valvular disease in childhood remain for a long time entirely latent. It is, in fact, often astonishing to find well marked physical signs of valvular disease in a child who complains of no more than anorexia or slight cough.

The physical signs themselves are approximately the same in adults and children. In general, murmurs are louder in children, and one is much less prone to discover endocarditis without a murmur in childhood (Hochsinger). Murmurs are transmitted over the chest more commonly in children, and probably owing to the small size of the thorax are well heard posteriorly, especially to the left of the spine.

The strength of the cardiac muscle is remarkable with the result that the heart adapts itself easily to excessive strain by marked hypertrophy. The *cor bovinum* is therefore not uncommon. The overacting heart causes deformity of the more pliable chest wall, so that, in children, protrusion of the precordium is a not infrequent result.

Marked arrhythmia is very much more uncommon than in adults.

Mitral insufficiency is the most common of the valvular diseases. It is characterized by left-sided hypertrophy and is accompanied by a loud blowing systolic murmur, best heard over the apex, and transmitted toward the axilla, and heard to the inner side of the left scapula. A systolic thrill is occasionally present. About one-third of the cases are uncomplicated, the remainder are associated with stenosis.

Among the various valve defects, mitral stenosis holds a rather interesting position. Compared with insufficiency, mitral stenosis is an uncommon condition. It is rarely present alone, being usually

associated with regurgitation. Following the lead of Duroziez, the French lay great emphasis on the occurrence of so-called "pure" mitral stenosis. Under this name Duroziez, in 1877, described a group of cases with the following characteristics: "Pure mitral stenosis, *i.e.*, without a murmur of insufficiency, without much dilatation of the auricle, without lesion in the lung, is more frequent than was believed. It is easily overlooked, the patients being troubled very little and having in no way the appearance of cardiacs. The heart is normal in size and impulse. The pulse is regular. Pallor is remarkable. The first sound is strikingly loud. The onset is often difficult to fix and may go back to infancy. One often fails to find the history of any acute disease. It is commoner in women. It is compatible with long life."*

The subject of mitral stenosis is still further complicated by the views of French clinicians who ascribe its origin to the toxic action of diseases such as tuberculosis or syphilis on the growth of the heart, thereby placing mitral stenosis more or less in the class of congenital defects. Thus Fournier says: "What has been termed 'pure mitral stenosis' is not a stenosis resulting from a pathological process, as for example, a fetal endocarditis, as was originally supposed; it is, on the contrary, a primary independent lesion, a congenital malformation, proceeding from an arrest in development."† Huchard may also be quoted in this connection as follows: "Pure mitral stenosis is neither the result of a fetal endocarditis, nor of an infantile endocarditis, nor of a marginal valvulitis of tuberculous origin. Hereditary tuberculosis, and especially hereditary syphilis, as well as all cause of degeneracy, may produce congenital mitral stenosis by cardiac malformation which is the result of an arrest of development, that is to say, the persistence of the union of the valvular apparatus."‡

In spite of the above views we are loathe to accept the idea that pure mitral stenosis should be regarded as a developmental defect, even though any preceding inflammatory process seems conspicuously absent. In all probability syphilis is a cause of cardiac disease, but its importance in the pathology of the heart in children should not be overestimated. We have had Wassermann reactions performed upon a large number of children suffering from valvular disease, but have seen only a single positive result—in a case of adherent pericardium.

Besides being attributed to the action of toxin on the heart, mitral stenosis has also been ascribed to congenital heart disease. A careful search of the literature, however,§ has convinced the writer that though mitral stenosis has rarely been observed at autopsy in infants, and though it also occurs in children over five years of age in whom there is present no apparent etiological factor, there is no

* Duroziez, Arch. Generales, ii (1877), p. 32.
† Fournier, Recherché et Diagnostique de l'Heredo Syphilis Tardive, p. 237.
‡ Huchard, Maladies du Coeur (1910), p. 313.
§ Bass, Arch. Ped. (Feb., 1916).

justification for the term "congenital mitral stenosis" as applied to the disease in older children. If mitral stenosis were the result of congenital disease, one should be able to find reports of its presence at autopsy in young children. Such, however, is not the case, as there are no cases reported under five years of age, excepting a few infants dying within the first few hours of life.

The physical signs of mitral stenosis consist of evidence of right-sided enlargement of the heart. At or within the apex there is to be

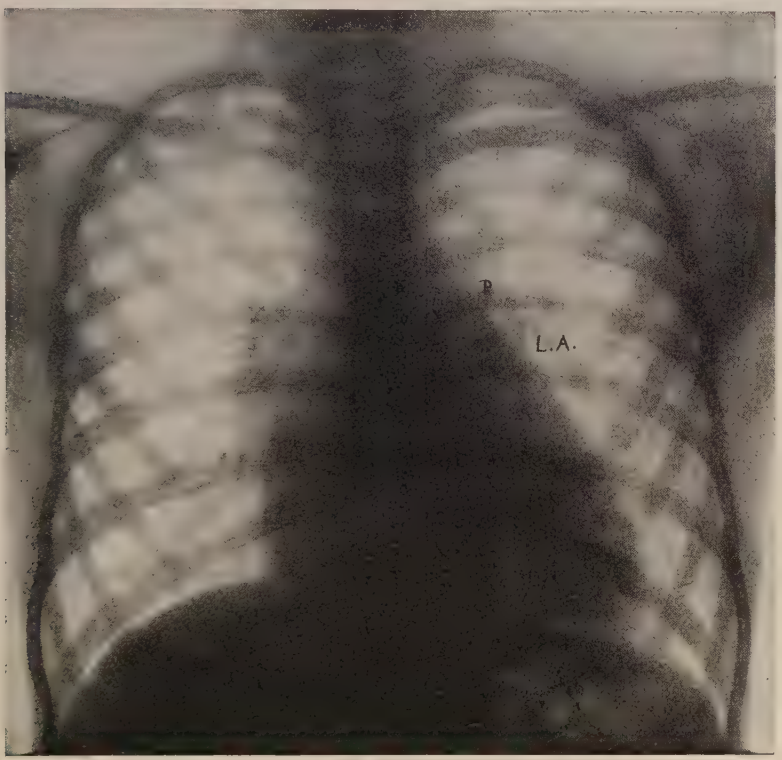

FIG. 122.—Radiogram: Heart in chronic mitral disease. Note the characteristic bulging caused by the pulmonary artery *P.* and the left auricle *L.A.*

felt a presystolic thrill, and there is heard a loud rough rumbling murmur presystolic in time and ending with an appreciable snap corresponding to systole.

One of the results of any valvular lesion, but especially of the stenoses, is a retardation in the growth of the body. The child remains small and backward, being several years behind in its mental and physical development. Such cases have been described under the name of Cardiac Infantilism or Dwarfism.*

* Bass, *loc. cit.;* Gilbert and Rathery, Presse Méd., viii (1900), pp. 225, 231; Weber, Brit. Jour. Dis. Child., x (1913), p. 203.

Aortic insufficiency is uncommon. It is characterized by the same physical signs as in adult life—enlargement of the heart to the left, and the presence of a blowing diastolic murmur loudest over the second interspace to the right of the sternum and transmitted downward to the left. The pulse is of the water-hammer type. Capillary pulse and pistol-shot sound may be present.

Aortic insufficiency is never present alone. It is a very serious form of valvular disease in children, most of the cases succumbing before the age of puberty. Sudden death may occur.

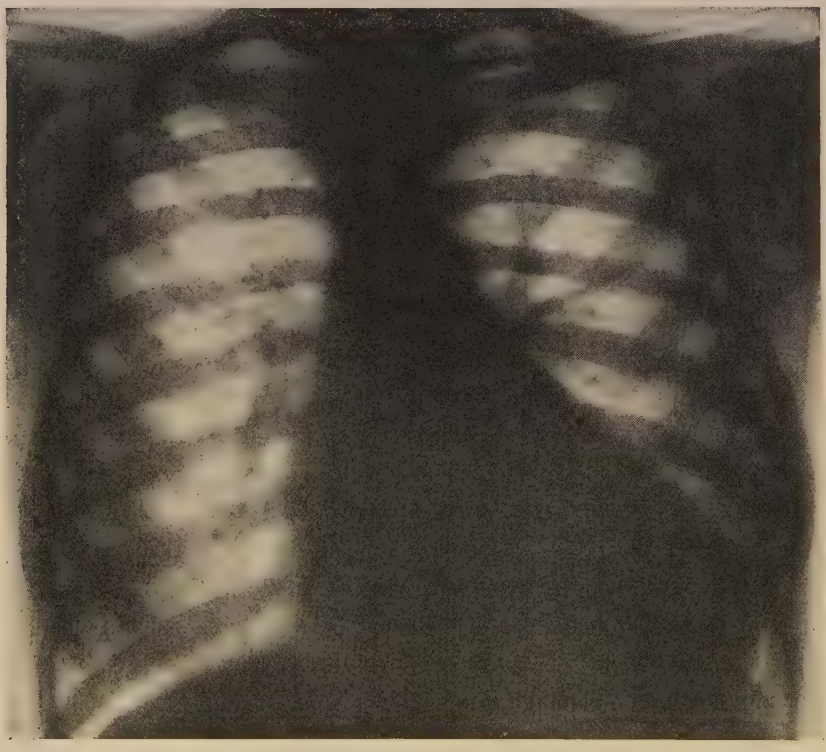

FIG. 123.—Radiogram: Heart in aortic insufficiency. Note the extreme lengthening of the long axis of the heart approaching the horizontal in position.

Aortic stenosis is more often due to congenital than to acquired heart disease. It may be associated with insufficiency and is recognized by the presence of a loud rough systolic murmur best heard over the second right interspace, and transmitted upward over the carotids; marked hypertrophy of the left ventricle; and a rough systolic thrill over the aortic area.

The tricuspid valve becomes insufficient in cases of marked mitral disease when dilatation of the right ventricle takes place. This lesion is a relative one and as a rule not due to valvular inflammation. It is characterized by the presence of a systolic murmur loudest over the lower portion of the sternum. Signs of marked stasis are present

(systolic pulsation of the neck veins, venous engorgement of the liver, etc.).

Tricuspid stenosis, pulmonic regurgitation and stenosis are practically only found as congenital lesions.

The Roentgen examination of the heart in valvular disease shows characteristic silhouettes depending upon the location of the lesion. Mitral disease reveals prominence of the shadow of the left auricle which may be seen to show abnormal pulsation (Fig. 122). In aortic insufficiency the heart appears to assume a more horizontal position and the ventricular hypertrophy causes the apex of the heart shadow to be blunt and rounded (Fig. 123).

Circulatory Failure.—As soon as the heart loses its ability to maintain an efficient circulation of the blood, a certain group of symptoms appear which may be discussed under the head of Circulatory Failure. Although we are describing these symptoms under the head of Valvular Disease, it must be understood that any condition causing failure of the cardiac mechanism may lead to the same result. Such conditions are pericarditis, both acute and chronic, and myocarditis. Whooping cough, when very severe, may by the great strain imposed upon the heart lead to cardiac insufficiency (Hochsinger). Occasionally pulmonary diseases, as severe asthma or emphysema, lead to dilatation of the heart and symptoms of broken compensation. Pulmonary disease, however, is much less often a cause of heart disturbance in childhood than it is in adult life. The same may also be said of diseases of the blood vessels and the kidney, for though the heart is involved in nephritis, so-called cardiorenal disease is unknown in childhood.

As in adult life, the chief symptoms of cardiac failure are due to stasis. However, edema of the extremities is not uncommon in children nor does it appear early. Much more prominent is enlargement of the liver and stasis of the portal circulation. This may appear as the first sign of failing compensation and as the heart becomes less and less able to maintain the circulation, ascites gradually supervenes. At the same time there are signs of beginning congestion at the bases of the lungs—râles, dulness and changed breathing. In severe cases hydrothorax results.

The heart at this time shows distinct changes. Cardiac dulness increases as the heart dilates. Relative tricuspid insufficiency may appear. The pulse becomes rapid and weak, but arrhythmia is unusual. Herein lies an important difference between the child and the adult—for whereas in the latter continued disturbances of the heart rhythm, as auricular fibrillation, are very common, in the child they are extremely rare. In failing compensation in the course of nephritis, gallop rhythm or embryocardia may be present, but they do not belong to the usual picture of broken compensation in the course of valvular disease.

Course and Prognosis.—As a rule when once a heart valve has become the seat of inflammation that valve remains permanently

diseased. However, there are numerous cases on record where relatively long-standing cases have gone on to apparent cure. In general, it may be said that the prognosis depends first, on the location and type of the lesion, second, on the general nutrition of the child; third, on the presence or absence of complications and lastly, on the condition of the heart muscle.

As to the first point, mitral lesions are much better borne than those of the aortic valve. Mitral insufficiency is the least dangerous of the valvular diseases and is compatible with long life. Mitral stenosis, on the other hand, is much more serious. Aortic insufficiency is a very dangerous lesion, few children suffering from it passing the age of puberty.

The general condition of the child is important, because if in good health it is more likely to withstand secondary attacks of rheumatism, and moreover, if the general nutrition is good, the myocardium is more liable to remain healthy.

The complication most to be feared is pericarditis, an acute attack of which always reacts badly upon the heart muscle. Pericardial adhesions also lead to dilatation and consequent decompensation.

Since, as has been previously pointed out, the child's heart is endowed with great powers of resistance, it follows that when signs of cardiac failure appear, the condition must be considered a very grave one. According to Hutinel* a child rarely survives the first severe break in compensation for longer than two years, and in the more acute cases death occurs within three or four months. In making a prognosis, however, one should never forget the recuperative power of the juvenile heart, and though the ultimate outcome be fatal, the immediate prognosis is not necessarily bad, and temporary recovery may take place, as in the following case:

A girl, aged 10 years, who was known to have had cardiac disease for three years past, suffered a severe break in compensation due to an active attack of dry pericarditis following acute tonsillitis. Examination revealed a markedly dilated heart; pulse extremely rapid and of poor quality; signs of mitral stenosis and insufficiency; dry pericarditis; left-sided hydrothorax sufficiently pronounced to require paracentesis; liver one hand's breadth below the free border of the ribs; marked ascites; diminished amount of urine with albumin and casts; temperature up to 103; great restlessness; cough and cyanosis.

In spite of this ominous picture, the child, under appropriate treatment, improved rapidly. Six months later she was able to return to school and the heart was apparently well compensated.

In general, it may be said that the great danger to the child with a valvular defect lies not so much in a break in compensation, as in repeated attacks of acute endocarditis. Dunn† has shown this very clearly in a study of a series of 264 children who were followed for a period of 10 years. Symptoms referable to acute inflammation of the

* Les Maladies des Enfants, Paris (1909).

† Amer. Jour. Dis. Child., vi (1913), p. 104.

heart were encountered much more frequently than symptoms of decompensation, and in the great majority of cases it was the recurrent acute attacks which caused death. Childhood is the dangerous age, for during that period attacks of acute rheumatism are much more frequent than after puberty. From this it follows that if the child survives the age of puberty without having had recurrent attacks of acute inflammation, the outlook is good. It is particularly at the age of rapid development from the eleventh to the fourteenth or fifteenth year that we meet with cardiac accidents. When this time of stress, however, is over the heart usually accommodates itself well.

"The immediate mortality of rheumatic cardiac disease is about 20 per cent. The subsequent mortality of patients with endocarditis of rheumatic origin, followed for at least 10 years, is about 50 per cent. . . . The mortality is seen chiefly during childhood. The mortality after young adult life is reached falls to only 7 per cent."*

Treatment.—The treatment outlined for acute pericarditis applies also to acute endocarditis. Here too we must emphasize the importance of complete rest in bed, the ice bag to the precordium, the exhibition of salicylates in the rheumatic cases, and the use of sedatives (bromides or opium) in the restless toxic cases.

Bed rest must be insisted upon long after all the acute symptoms have disappeared (four to six weeks) and exercise, even of the mildest type, should be begun with the greatest care and moderation. After recovery from the febrile stage, and after a thorough course of rest treatment, the child still needs continued attention. In the great majority of cases, acute endocarditis is followed by permanent valve damage, and it becomes the duty of the physician so to regulate the life of the child that a minimum strain is put upon the heart.

A child with a valve defect should be examined at regular intervals. Its activities must be restricted so as to avoid very violent exercise, such as athletic contests or races. It is, however, a mistake to forbid all exercise to children whose hearts are well compensated, for moderate exercise, such as calisthenics or bicycle riding, probably improves the condition of the heart muscle. Excessive stair climbing should be prohibited.

The general hygiene must be of the best. The diet should be supervised so as to exclude attacks of indigestion or constipation. The child should, if possible, rest for a short period every day. Anemia should be watched for and treated when present. Colds and sore throats must be guarded against, and hypertrophied tonsils removed. Unless there is distinct decompensation, the operation of tonsillectomy under general ether anesthesia is advisable, even in children with well marked valvular disease, since the risk of reinfection of the endocardium through the tonsils is much greater than the risk of an accident due to the operation itself.

The question of prophylaxis in children with valvular disease becomes all the more important as the age of puberty is approached,

* Dunn, *loc. cit.*

because the strain on the heart due to the rapid growth of the developing organism is very likely to predispose to failure of compensation. As the age of puberty is passed, the question of choosing a trade or profession must be answered, and one should advise strongly in favor of occupations in which there will be little likelihood of over-exertion. At the present time the establishment of special cardiac clinics both for children and adults is directing attention to this important consideration and is laying distinct emphasis upon the conservation of the heart by the prevention of reinfection or broken compensation.

At the first sign of failure of the circulation, such as breathlessness, cough, palpitation, tachycardia, enlargement of the liver, cardiac dilatation, etc., the child should at once be put to bed. It is remarkable to note how much improvement may follow rest alone. The ice bag to the precordium, as advised in acute pericarditis, is also of great use here in slowing the pulse rate. If there is orthopnea a suitable back rest should be provided, so that the child may remain in a semi-reclining posture even during sleep. The diet should be very bland—solids as a rule being better borne than fluids. They should be selected so as to avoid any foods likely to produce flatulence, and are best given in small amounts at frequent intervals.

The enlarged liver and the congested portal circulation require catharsis. Calomel may be given at the outset and repeated, if necessary, every week. Magnesium sulphate or other saline should be administered every morning until the congestion of the liver and ascites or edema have disappeared.

We are also able to improve the circulation by directly strengthening the muscular power of the heart itself by means of drugs. The digitalis group is of great use, in spite of the fact that the chief indication for its use in adults, auricular fibrillation, is almost never present in childhood. However, when there are signs of cardiac dilatation with rapid pulse and consequent stasis, digitalis is extremely useful. It may be administered either in the form of the tincture or, when diuresis is especially desired, in the form of a freshly made infusion. The dose varies according to the age of the child—5 to 10 minims of the tincture, or 1 to 2 drams of the infusion may be prescribed three or four times a day to a child of 10 years of age. In some cases where these drugs disagree with the digestion, digalen (Cloetta) may be employed in the same doses as the tincture. Digipuratum is also very useful. Tincture of strophanthus has been highly recommended for children, but is probably of little value. At present it seems proven that the oral administration of strophanthus is useless and that it is only effective when given intravenously. The latter method has given striking results where rapid cardiac stimulation was needed, but it is fraught with considerable danger, especially if the case has been under very recent digitalis therapy. One must be guided as to how long to continue these drugs by the results obtained—a lowering of the pulse rate and an increase in the amount of urine excreted are signs that we have obtained the

desired action and the dosage should be substantially reduced. This is important on account of the cumulative action of these drugs.

In cases of cardiac insufficiency in which the pulse is slow, one cannot expect the rapid response to digitalis obtained in those with rapid pulse rates. This is particularly true where there is great portal stasis with large liver and ascites, for in such cases the drug is probably very poorly absorbed. In this condition the previous use of a modified Karrel diet will be found of value. After a few days of strict limitation of the fluid intake, digitalis may suddenly be found to be effective where previously it had been inert (Janeway).

It is particularly in the cases of broken compensation with edema or ascites that the most brilliant results are obtained with digitalis. The diuretic effect may be heightened by the use of theocin or diuretin, the latter especially giving excellent results.

In acute collapse, hypodermic injections of camphor or caffein should be given. Strychnin, though much used, has probably very little use in the doses usually employed.* Where rapid action is desired a single intravenous injection of digalen is useful (1 c.c. of digalen diluted with a few cubic centimeters of normal salt solution for a child of about 10 years).

Where the heart action is very rapid and there is great distress and dyspnea, codein or morphin hypodermatically are indicated. This is particularly useful where children are brought to the hospital badly decompensated—for the excitement of new surroundings and the commotion caused by transportation often cause very urgent symptoms. In such cases the administration of morphine will allow the child to quiet down and give time for the cardiac tonics to take effect.

Occasionally marked edema of the legs which resists purgation and diuresis may be much benefited by multiple small incisions through the skin which allow the fluid to drain out into dressings. Ascites may require abdominal paracentesis, or persistent hydrothorax will call for thoracic puncture.

Venesection, though recommended by some, is not of great use in children. On the other hand, the engorgement of the liver may be favorably influenced by the application of several leeches over the right hypochondrium.

If the acute symptoms of cardiac decompensation have been overcome, and the patient is able to be up and about again, a tendency to tachycardia or breathlessness may remain in spite of prolonged rest treatment. In such cases the continued or interrupted use of digitalis will be found very beneficial. Small doses of tincture of digitalis should be taken twice daily for a period of two weeks to be followed by two weeks without the drug. This alternation may be continued for a long period of time, and will be found to do much to keep the heart in good condition.

The treatment of bacterial endocarditis is chiefly symptomatic. In the acute cases death usually occurs before treatment has a chance

* Lucas, Am. Jour. Dis. Child. (1914).

to be of much avail. In the subacute cases, autogenous vaccines, made from the organisms obtained from the blood cultures, may be tried. Antistreptococcus serum has been advised, also the transfusion of normal human blood. In the great majority of cases, however, the relief, if there is any, is only temporary and the case goes on to a fatal termination.

ACCIDENTAL MURMURS AND "FUNCTIONAL" CARDIAC COMPLAINTS

Through an unfortunate terminology we have become accustomed to classifying cases of cardiac disease into an "organic" and a "functional" group. However, as well stated by Jacobi, "the diagnosis of deranged function in any organ is only a makeshift, and justifiable only as long as we are ignorant of the physical cause of the derangement. A functional heart murmur is one, the anatomical cause of which we do not know. That is why a skilled diagnostician may recognize fewer functional murmurs than one who will not diagnosticate a heart disease unless he has all the symptoms, including dilatation and hypertrophy."* It has therefore been the purpose of cardiologists to eliminate as many as possible of the so-called "functional" cases, assigning to them well-founded organic causes. Thus we may see in the chapter on the affect of growth on the heart that certain symptoms formerly considered functional are in reality due to a change from the normal in the shape and position of the heart. In the same manner the cardiac arrhythmias have quite recently been analyzed and classified, with the result that a distinctly demonstrable organic basis has been found for various so-called functional irregularities.

Although at the present time most of the text-books still adhere to the term "functional murmur," we prefer to discard it and substitute "atonic," "hemic," "cardio-pulmonary" or "accidental" depending upon whatever we believe to be the underlying cause of the murmur.

This subject is of importance since by far the larger majority of children seen by the pediatrist for complaints referable to the cardiovascular system are precisely those in whom it is difficult to find so-called organic heart disease. Murmurs heard over the precordial area in childhood should therefore be studied with the greatest care before a final judgment as to their causation is arrived at. Unquestionably more than half of these murmurs do not depend upon inflammatory changes in the heart muscle or valves, and hence would previously have been classified as functional.

The majority of such murmurs are cardio-pulmonary in origin, and hence may be found to vary in intensity with the phases of respiration, being loudest at the end of inspiration and faintest at the end of expiration. As the cardio-pulmonary murmur originates outside the heart, change in the posture of the child, by altering the relation of the heart to the surrounding viscera, may alter the character of the murmur and even cause its complete disappearance. In the same manner pressure

* Trans. Amer. Climatol. Assn. (1899), p. 241.

of the stethoscope may alter the loudness of such murmurs. Schlieps* has emphasized the importance of the time in the cardiac cycle at which these murmurs occur. He believes that functional murmurs in contra-distinction to organic ones take up only part of the systole, usually the middle third. He therefore calls them mesosystolic, emphasizing this as characteristic of the cardio-pulmonary murmur. However true this may be theoretically, it is very difficult to appreciate on auscultation.

The same author uses the term "atonic" for the murmurs found over the hearts of asthenic children. This murmur is heard usually over the region of the apex, differing in this respect from the cardio-pulmonary murmur which is heard as a rule over the base of the heart. The atonic murmur is supposed to be due to a relative insufficiency of the mitral valve following a loss of tone of the heart muscle. It is not affected by change of posture or pressure of the stethoscope, or by deep breathing. This murmur may, however, disappear after fright or marked psychic disturbance.

Although variability must be admitted as a characteristic of these murmurs, we may meet with cases of myocardial or endocardial disease in which the loudness of the murmur undergoes considerable change from day to day. In fact, cases of true organic disease have been described in which well-defined murmurs have completely disappeared though the diagnosis of organic disease has been corroborated by autopsy.†

Hochsinger‡ is responsible for the general impression that accidental murmurs are unknown in early life. Authorities are now, however, agreed that even in young infants there may be heard both over the base and the apex soft blowing systolic murmurs which persist for a period of months or years to disappear without apparently leaving a trace of any deleterious effect on the heart.

In making the differential diagnosis between an accidental and an organic murmur, the following points must be considered:

1. The nutrition of the child: Hemic and atonic murmurs in the anemic child.

2. The type of child: Atonic and cardio-pulmonary murmurs in the asthenic child.

3. The shape of the heart shadow as seen with the fluoroscope: Presence of mitral shape or signs of ventricular hypertrophy in favor of organic murmur.

4. The murmur itself: Character; time of occurrence; location over the precordium; variability; influence of pressure or change of posture.

5. Presence or absence of other signs of acquired or congenital heart disease: Accentuation of the second pulmonic sound in early mitral cases especially important.

* Jahrb. f. Kinderh., lxxvi (1912), p. 247.
† Musser, Brit. Med. Jour., ii (Oct. 16, 1897), p. 1055.
‡ Arch. f. Kinderh. (1913).

Children in whom such accidental murmurs are found frequently present no subjective symptoms whatever, or they show symptoms of cardio-vascular instability. Sudden attacks of flushing and faintness coupled with rapid pulse and palpitation appear. These paroxysms may come on after fright, exertion or errors in diet leading to flatulence and overdistended stomach. Headache, vertigo and general irritability are common. To these must be added pallor which may be due to a true anemia, or more often may be simply the result of vascular disturbance. Among the latter cases will be found those children who show pseudosclerotic arteries and whose pallor is probably due to vasoconstriction of the vascular supply of the skin, as the hemoglobin estimations show normal values. Morning vomiting, especially in children who hurry to school (Heubner), is often observed.

The prognosis in these cases is good. As a rule the symptoms are lost with the advent of puberty. The importance of these symptoms lies in the fact that they so closely resemble those of inflammatory heart disease.

The treatment of children showing these functional disturbances should be along the lines of general hygienic care. Excitement and over study should be avoided. The diet should be supervised with special care—tea, coffee and alcohol being forbidden. Very often psycho-analysis will reveal some repressed thought, the discovery of which and its explanation will go far toward clearing up the heart symptoms. Such are the cases in which masturbation plays a rôle.

Drug treatment consists mainly in the use of tonics and hematinics. In those cases in which vascular symptoms are prominent, belladonna administered in fairly large doses may be found useful. During the attacks of palpitation, bromides and aromatics should be given.

DISTURBANCES OF THE CARDIAC RHYTHM

In recent years the development of the polygraph and the electrocardiograph have permitted a much more careful study of the cardiac irregularities, so that at the present time we are able to place so-called "irregular hearts" into very definite groups. Moreover the application of these graphic methods to the study of the hearts of children has conclusively demonstrated that, though the various forms of arrhythmia are of less frequent occurrence in childhood, nevertheless most of the better known types seen in adults are represented. Arrhythmias are in general less frequently found in children probably because chronic sclerotic processes which damage the heart muscle are so much less commonly encountered. The most important disturbances in cardiac rhythm found in children are the following:

1. Sinus arrhythmia.
2. Simple tachycardia.
3. Paroxysmal tachycardia (auricular flutter).
4. Auricular fibrillation.
5. Premature beats, (*a*) auricular, (*b*) ventricular.
6. Heart block.

Sinus Arrhythmia

This is by far the commonest form of juvenile irregularity. It is due to a variation in the length of diastole with the result that several heart beats, following each other in quick succession, are succeeded by a group of beats at a slower rate. The record of each individual beat is a normal one, showing that the impulse has originated from the normal site and has spread through the cardiac tissue in a normal manner. The condition arises from changes in the vagus impulses which result

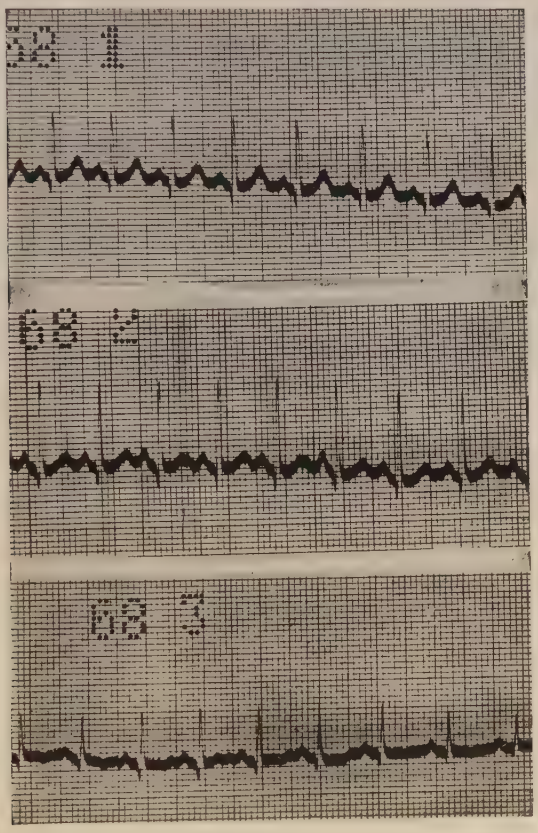

Fig. 124.—Electrocardiogram of normal child.

in the heart as a whole beating at different rates at varying times. Moreover simultaneous records of the pulse and the respiration corroborate this fact; for the more rapid phases of the cardiogram are found to coincide with inspiration, while the slower ones are coincident with expiration. In marked cases this fact may be demonstrated by feeling the pulse and at the same time having the child take deep breaths—the pulse will be felt to accelerate during inspiration and to slow down during expiration. For this reason this form of cardiac irregularity is known as respiratory or vagus arrhythmia (Figs. 124, 125).

Very marked varieties of sinus arrhythmia may perhaps be considered as bordering on the pathological; but this type of irregularity is found to a slight degree in practically all children, so that it is spoken of as a physiological irregularity. It increases both in frequency and extent as the age of the child increases, until at puberty it is almost universally present and often extremely marked. Mackenzie has described this as the "youthful type of irregularity" and has called attention to its frequent presence in cases of his so-called X-disease, or juvenile neurasthenia.

Apparently sinus arrhythmia is unusual during early life and becomes more frequent in older children on account of the rapid pulse rate of the younger children; for it is easy to demonstrate that the irregularity may be made to disappear by increasing the heart rate. It is a not infrequent occurrence for a child, especially one about the age of puberty, to be brought to the physician for cardiac irregularity,

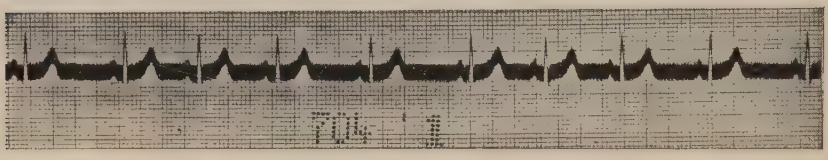

FIG. 125.—Sinus arrhythmia (respiratory). Note the rhythmical acceleration and retardation of the rate.

when a few moments of rapid calisthenic exercises at once causes the pulse to become regular.

Swallowing also affects this form of irregularity.

The heart beats may be so irregular that the child notices the condition himself and comes complaining of palpitation and a sense of fluttering in the region of the heart.

It is very important to bear in mind that irregularity of the heart is a normal condition in the growing child since many parents have been unduly alarmed by being told that their child was suffering from "heart disease" when in reality the condition present was only sinus arrhythmia. In fact Mackenzie goes so far as to say that the presence of sinus arrhythmia, especially after an acute illness, is of good omen, for according to him this means that the heart is particularly strong. Hecht* also comments on the fact that he never found sinus arrhythmia in children who were suffering from severe heart lesions either congenital or acquired.

In diagnosing this condition the child should be asked to take deep breaths, when the irregularity at the pulse will be brought out more clearly. Following this the child should take some rapid exercise, as suggested above, when the irregularity if due to sinus arrhythmia will diminish or entirely disappear. As a final test, though rarely necessary, atropin may be administered, following which the irregularity will disappear owing to the blocking of the vagus impulses.

* Ergebnisse fur Inn. Med. u. Kinderheil, xi (1913).

From the foregoing it will be evident that this condition needs no treatment *per se*, though when present in high-strung, neurotic children about the age of puberty, it should be looked upon as one of the manifestations of nervousness, and the appropriate treatment for that condition should be instituted. Under no circumstance should exercise be forbidden on account of the heart irregularity alone.

Simple Tachycardia

Under this heading are included cases of rapid heart in which the pulse tracings or electrocardiograms reveal no abnormality in the heart mechanism except increased frequency of the beat. Rapid pulse may be due to nervous influences, hyperthyroidism, to conditions in the heart muscle itself and to increased demands upon the circulation. In childhood it is not unusual to meet with cases of rapid heart, especially among older children who are high-strung and neurotic. Such

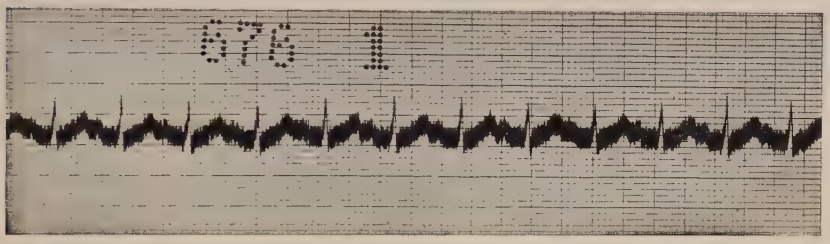

Fig. 126.—Simple tachycardia. (Exophthalmic goiter.) (Girl aged thirteen. Pulse rate about 135 per minute.) Note the fine oscillations, known as "splintering," which are due to muscular tremor.

children become nervous during examination and their pulse rate rapidly increases. To a pulse of this type the term labile has been applied.

By "labile" pulse we must understand not only one which after exertion becomes extremely rapid, but also one which becomes very small, so as to be felt at the wrist with difficulty. The response of the pulse rate to exercise has been used as a rough estimate of cardiac efficiency, but in a study of children suffering from orthostatic albuminuria, it was shown that normal healthy controls evinced the same tachycardia after running up several flights of stairs as did those children whose cardiovascular systems were supposedly weak.* Mere rapidity of the pulse in childhood, therefore, must not be used as a test of the cardiovascular efficiency. On the other hand, when the pulse after exercise becomes not only rapid, but also loses its good quality, so as to become thready and at times almost imperceptible, we may conclude that we are dealing with an unstable circulatory system.

Simple tachycardia is associated with fever, with exophthalmic goiter (Fig. 126), and with certain disturbances of nutrition. To the

*M. H. Bass and H. Wessler, Arch. Int. Med., xi (1913), p. 403.

last named group belong the cases of tachycardia in children showing latent scurvy.* Such infants may continuously show pulse rates of 150 to 200 and apparently be quite contented and comfortable. The pulse rate may be reduced by feeding anti-scorbutic food.

Whether the tachycardia seen as a rare complication of tetany belongs to this group or whether it should be classed under the head of paroxysmal tachycardia is not decided. As will be seen below, the paroxysmal tachycardias are characterized by the fact that the cardiac impulses do not arise at the normal site. No reports of tetany cases are to be found which have been studied with the electrocardiograph during the period the pulse was rapid, and we are therefore ignorant of the exact cardiac condition. We have had cases of carpopedal spasm studied electro-cardiographically, but no abnormality was found. This agrees with the findings of Hecht. Finkelstein (quoted by Hecht) has seen the pulse of an infant suffering from tetany suddenly go up to 200 after a gastric lavage. We have seen an infant in whom typical tetany with carpopedal spasm and laryngismus was ushered in by a sudden attack of extreme tachycardia. Although this case was not studied with the electrocardiograph, the sudden onset and abrupt cessation of the tachycardia make it very probable that we were dealing with the paroxysmal variety.

Paroxysmal Tachycardia (Auricular Tachysystole)

By paroxysmal tachycardia we understand a condition characterized by sudden attacks of very rapid heart action. Furthermore the cardiac impulses in these cases do not originate in the sinus node, but in some other part of the heart tissue, as is shown by the electrocardiographic records. These cases have been divided into two groups: First "paroxysmal tachycardia" in which the auricular rate is under 200, and second "auricular flutter" in which the auricular rate is above this figure. When cases of the last mentioned group were studied in adults it was found that owing to the great rapidity of the auricular contractions, the ventricle was usually not able to keep pace with the auricles, and a condition of partial block resulted. Thus the auricle might be beating at 280 while the ventricle beats at 72—a condition of 4 : 1 heart block. In children, however, it has been recently observed that even when rates typical of auricular flutter existed, the ventricle was able to respond to each beat, so that ventricular rates approximating 300 were maintained.

From the above it will be evident that we cannot use the same diagnostic points to differentiate paroxysmal tachycardia and auricular flutter in childhood which we use in adults, and we probably do best to include both conditions under the term "Auricular tachysystole" as suggested by Wilson.†

The cause of these attacks of rapid pulse is not at all clear. Some of the cases, as for example that of Hutchinson and Parkinson,‡

* A. F. Hess, Jour. A. M. A., lxviii (1917), p. 235.
† Amer. Jour. Dis. Child., x (1915).
‡ Brit. Jour. Dis. Child., xi (1914), p. 241.

occur in previously perfectly healthy children; others* are found in children suffering from rheumatic carditis or diphtheritic myocarditis.† Contrary to the condition in adults, the great majority of the cases in children occur in individuals free from valvular disease. Moreover as most of these cases recover, autopsies are few, with the result that the pathology of the condition is not very clear. In one of Hume's cases following diphtheria, post-mortem examination revealed a marked acute myocarditis, the auricles showing fatty degeneration and the ventricles interstitial inflammation and degeneration of the muscle fibers.

Apparently tachysystole may occur at any age. The youngest reported cases are one at 22 months‡ and one at 28 months of age.§

The attack starts in very suddenly accompanied by an abnormal sensation in the heart region. Occasionally there is vomiting and depression. Some of the paroxysms seem to follow directly on the child's bending forward to pick up an object, so that it has been suggested that compression of the heart may initiate an attack. In a case reported by Sutherland‖ a boy aged seven and one-half years experienced his first attack while seated quietly in a theater. The heart rate in this case, while the heart was unstable, could be influenced by tapping on the chest.

During the attacks the children as a rule complain very little, the subjective symptoms being much milder than in adults. There is usually some dyspnea and the child prefers to keep quiet, making as few unnecessary movements as possible. It is quite remarkable to see how comparatively comfortable these children are even when the pulse rate lies between 200 and 300; and it is interesting evidence of the wonderful adaptability of the child's heart to note how well the circulation is maintained in many of the cases in spite of the extreme tachycardia.

In a considerable number of the cases however, embarrassment of the circulation becomes evident, and this is especially so in those in which the duration of the attack is prolonged. In such cases there is marked increase of the cardiac dulness to both right and left. The child's color becomes dusky and cyanotic. The liver increases considerably in size and edema of the face and extremities appears. Ascites has also been described. The amount of urine is greatly diminished, and this together with the edema may lead to the mistaken diagnosis of nephritis. However in spite of this oliguria the urine may be entirely free from albumin and casts. In one case at the height of the attack there was bloody sputum.¶

Figure 127 is the electrocardiogram of a child aged three and one-half years, taken during a paroxysm and reported by N. W. Brown

* Sutherland, *Ibid.*, p. 337.
† Hume, Heart, v (1913), p. 25.
‡ Koplik, Amer. Jour. Med. Sci., cliv (1917), p. 834.
§ Zahorsky, Interstate Med. Jour., xxii (1915), p. 57.
‖ "The Heart in Early Life," London (1914).
¶ Merklen, Semaine Med., Paris, xxi (1901), p. 164.

who has collected all the cases (10 in number) that have been described occurring in childhood.*

The main objective features of an attack, besides the evidence of cardiac failure as just outlined, are the extremely rapid pulse as felt at the wrist and the excessively rapid pulsations of the neck veins. The latter phenomenon is very characteristic.

The duration of an attack may vary from a few hours to several weeks, and its cessation, like its onset, is very abrupt. An attack of

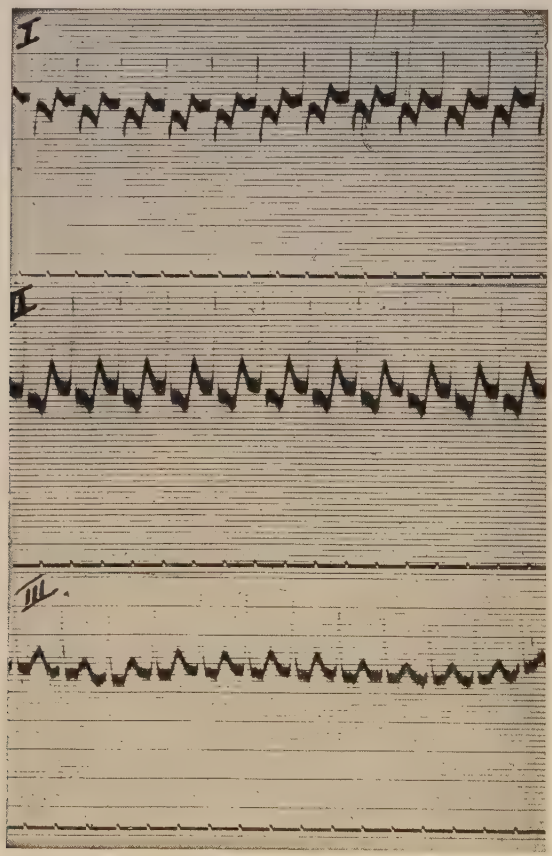

FIG. 127.—Paroxysmal tachycardia. Electrocardiogram taken during paroxysm. Rate 196.5 per minute. The P wave is represented by a deflection between S and T. (Case of Dr. N. Worth Brown, reported in American Journal of Diseases of Children, xiv, 1917, No. 4.)

vomiting may terminate the paroxysm, a fact of which advantage is taken in therapy; for induced emesis has at times been successfully used as a cure. After the attack is over the circulation rapidly returns to the normal—the pulse drops to normal, the dilated heart grows smaller, the liver diminishes in size, diuresis sets in. In certain

* Amer. Jour. Dis. Child. (Oct., 1917).

cases, instead of a return to normal, bradycardia appears and persists for a time. In other cases extrasystoles are common.

Not every case of tachysystole is easily recognized even in the midst of an attack, for there is no auscultatory evidence of auricular contractions, while the ventricular rate (and consequently the pulse) need not be much increased above the normal. The electrocardiogram will, however, invariably clear up the diagnosis by showing that auricular beats are occurring at an abnormally rapid rate.

The prognosis of tachysystole is fairly good provided the attacks do not come on too frequently and the heart muscle is not too severely affected. Many cases are reported in adults who have survived, though they trace the beginning of their malady back to childhood.

Treatment of this condition is not very efficacious. Many different drugs (belladonna, arsenic, bromids, adrenalin and the digitalis group) have been recommended, but with the exception of the last named are apparently of little use. Sutherland has used very large doses of digitalis (45 drops of the tincture daily to a boy of nine years) and believed that he hereby improved the circulation and diminished the pulse rate, though the heart entered upon a state of extreme irritability where it would pass suddenly from very slow to very rapid rates. Pressure on the vagus nerve in the neck has also been suggested.

Koplik who has published three cases with careful observations* warns against the use of digitalis. He believes the interval use of this drug is to be rejected on account of the ease with which heart block may be brought about, with disagreeably alarming symptoms. Digitalis should be used according to this author only in cases of imminent cardiac failure and collapse.

Auricular Fibrillation

Though so commonly encountered in adult life, auricular fibrillation is only rarely found in childhood. In most of the few cases that have been reported, acute rheumatism has been the cause.† An undoubted case developing during the course of diphtheria has been reported by Parkinson.‡ It may apparently be associated with heart block.§ Lewis has met with only four cases of fibrillation under the age of 20 years in a total of 116 cases. The rarity of its occurrence in early life may be partly explained by the fact that it almost never occurs in a heart previously healthy, but almost always in one the seat of long standing inflammatory disease.

Auricular fibrillation may be recognized clinically by the grossly irregular character of the heart beats, there being no semblance of any sort of rhythmicity at all. The electrocardiogram (Fig. 128) shows an absence of the P-wave, its place being taken by numerous oscilla-

* Amer. Jour. Med. Sci., cliv (1917), p. 834.

† Sutherland and Coombs, Heart, v (1913–14), p. 15.

‡ Heart, vi, 1 (1915), p. 13.

§ Price and Mackenzie, Heart, iii (1911–12), p. 233; Parkinson, *loc. cit.;* Nadel, Ges. fur Inn. Med. u. Kinderheil., Wien, xi (1913), p. 20.

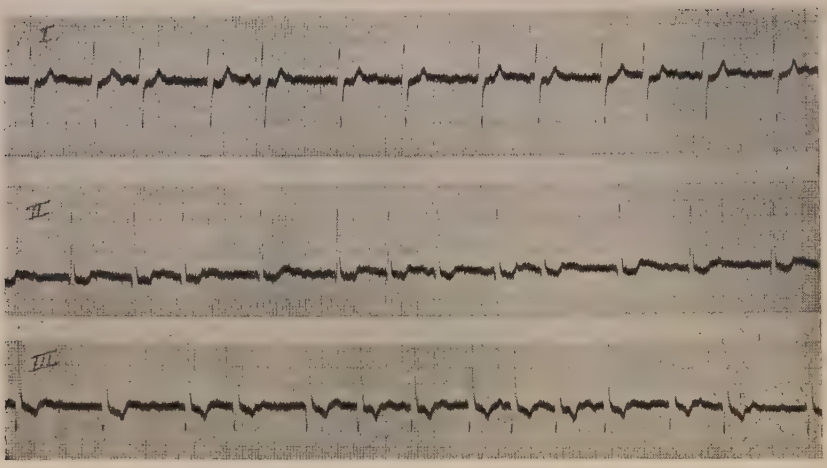

FIG. 128.—Auricular fibrillation. (Girl aged twelve. Chronic rheumatic valvular disease, mitral insufficiency and stenosis; chronic adherent pericardium.) Absolute irregularity. Note absence of P-waves which are replaced by irregular oscillations. (Case of Dr. B. S. Oppenheimer, electrocardiographed through the courtesy of Dr. H. B. Williams.)

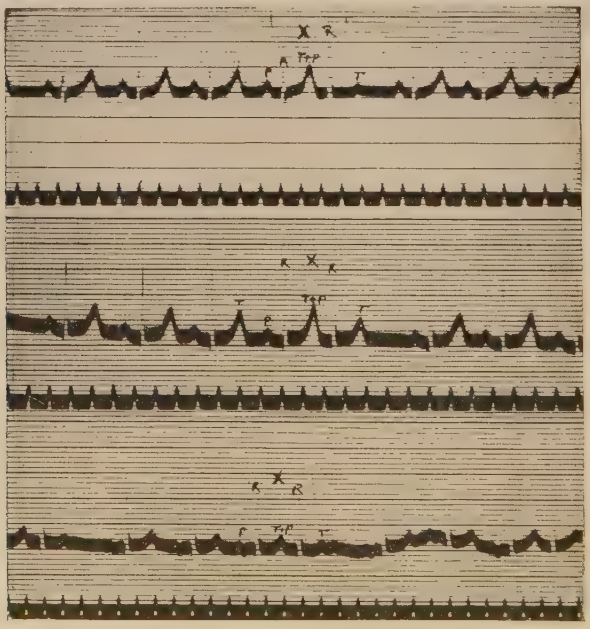

FIG. 129.—Premature beats of auricular origin. (Girl aged ten. Measles at 18 months. Tonsillectomy at four years. No illness since then. Complains of palpitation and dyspnea on exertion. Except for cardiac irregularity, physical examination is negative.) At X-the premature beats of auricular origin cause the P-wave to fall synchronously with the T-wave of the preceding beat, slightly changing its form.

tions, irregular in character, the result of the rapid fibrillary twitching of the auricular musculature. When the condition has once appeared it usually persists, hence its old name "pulsus irregularis perpetuus." Occasionally paroxysms of fibrillation have been found to last for a short time and then to give way to normal rhythm (Mackenzie).

The treatment of fibrillation consists in relieving the embarrassed circulation by the exhibition of digitalis. It is in the cases of fibrillation that the most striking results of digitalis therapy are encountered, for the drug appears to have a specific action in regulating the heart and thereby improving the circulation.

Premature Beats

Premature beats or extra-systoles are not a very frequent finding in childhood. This is contrary to the condition in adults where premature beats form a large percentage of cardiac irregularities. Their significance also appears to be different in childhood, for whereas they are usually of no very harmful portent in older individuals, in childhood they are often an indication of severe damage to the heart muscle.

There are three varieties of premature beats according to which portion of the heart initiates the impulse—auricular, atrioventricular and ventricular. Of these the first is most commonly found, the second less often, the last rarely* (Figs. 129, 130).

In a series of 120 cases of diphtheria examined with the polygraph, Gunson† found premature auricular contractions occurring singly and

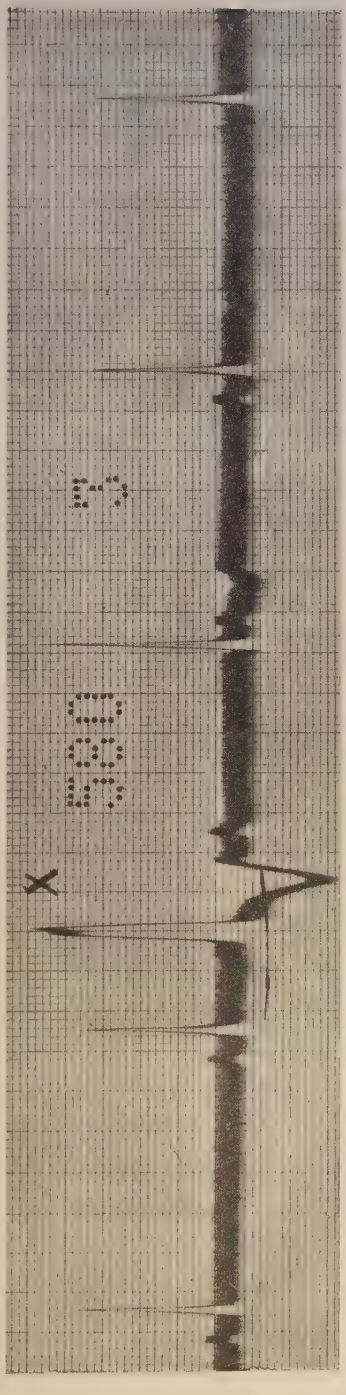

Fig. 130.—Premature beat of ventricular origin. (From the same case as Fig. 131.) Premature beat at "X." Curve also shows partial heart block.

* Wilson, *loc. cit.*

† Brit. Jour. Dis. Child. (Sept., 1914), p. 385.

infrequently in 28 per cent. of the children. They constituted the sole irregularity in the mild and moderately severe cases. He found no case of ventricular extra-systole in this series. Halsey,* in a series of 92 children showing cardiac irregularities, however, reports "premature ventricular contractions of varying origin."

There is considerable difference of opinion as to the prognostic significance of extra-systoles. Visco (quoted by Hecht) claims to have found extra-systoles 48 times in a series of 1000 children, including sick and healthy individuals. He believes that the irregularity is due to transient toxic functional disturbances, from which no conclusions as to the state of the heart muscle can be drawn. Hecht† absolutely disagrees with this view, and our own experience also leads us to consider extra-systoles of serious import when found in childhood. In diphtheria they may occur so frequently as to lead to very marked irregularity, and death from cardiac failure. We have observed two cases in which extra-systoles of auricular origin persisted for over a year after an attack of diphtheria. Wilson‡ well sums up their significance as follows: "Extra-systoles are much more serious when they occur before the tenth year and after middle age than when they occur during the intermediate period of life. They are also more serious when they occur in patients with other signs of cardiac disease than when such signs are absent. Extra-systoles as such are of little moment unless they are so numerous as to cause circulatory embarrassment, which is infrequent, and they require no special treatment. They are sometimes, however, the precursors of more serious disorders of the cardiac mechanism, and they may also indicate involvement of the myocardium."

Heart Block

Disturbances in the conduction system of the heart in childhood are not as rare as we had previously supposed. With the more thorough examination by means of the polygraph and the electro-cardiograph a number of cases of heart block have been discovered in children, even at a very early age, Eyster and Middleton having been able to collect 20 reported cases.§

Heart block may be defined as "an abnormal heart mechanism in which there is a delay in or absence of response of the ventricle to auricular impulses."‖ Normally impulses leading to contractions of the heart originate in the sinus node. They then pass downward to the auriculoventricular node and thence by the bundle of His and its two branches are carried through the Purkinje fibers to the ventricular muscle cells. The time consumed for the transmission of the impulse from the sinus to the rest of the heart has been determined and found to vary according to the age of the child. At birth and during early

* Arch. Ped., (Feb., 1917)
† *Loc. cit.*
‡ *Loc. cit.*
§ Am. Jour. Dis. Child., xix, p. 131.
‖ Lewis, "Clinical Disorders of the Heart Beat" (1912), p. 16.

infancy it averages 0.10 second in duration in early childhood this increases to 0.13 and at puberty it reaches 0.14 second.*

Any factor which disturbs the transmission of this impulse causes a lengthening of the conduction time which can be graphically recorded. In the phlebogram such a disturbance will cause a lengthening of the *a-c* interval, which on the electrocardiogram there is an increase in the distance between the P-wave which corresponds with auricular systole, and the beginning of the *I*RS group which represents the ventricular systole.

The varieties of heart block met with may be grouped under the headings (1) total heart block, where there is a complete dissociation, (2) partial heart block, where there is partial dissociation, and (3) delayed conduction, where there is no dissociation.† Anatomically

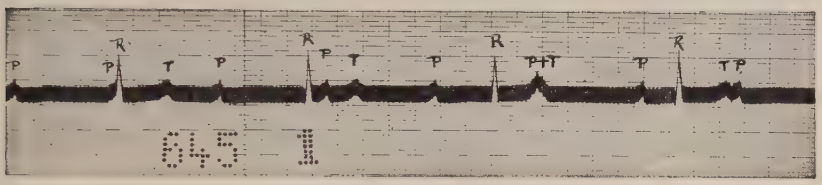

FIG. 131.—Complete auriculoventricular heart block. (Boy of fourteen, the subject of a congenital heart lesion. Pulse rate constantly 41 to 44 per minute.) Observe that the auricular P rhythm and the ventricular R rhythm each proceeds independently.

block is also divided into sino-auricular block, *a-v* bundle branch block and auriculoventricular block, the last named being the variety encountered in children. Block is also spoken of a "functional" when it is due to excessive vagus inhibition rather than to organic disturbance of the conduction system.

Contrary to the condition in adults, heart block is found in childhood to be due to the acute rather than to the chronic cardiac diseases. Whereas the common causes in adults are arteriosclerosis and syphilis, in children acute rheumatism, diphtheria and less often pneumonia are the chief etiologic factors. In certain cases congenital malformations of the heart have been advanced as causing block by direct involvement of the conduction system in a congenital defect. As in adults the excessive use of digitalis may lead to temporary block.

Post-mortem examination of hearts in which block has been observed have shown in most cases that the node and bundle were the seat of marked inflammatory and degenerative changes.‡ In other cases however the conduction apparatus was apparently structurally normal.§ The latter cases are explained as cases of toxic disturbance.‖

* Hecht, *loc. cit.*

† T. S. Hart, "Abnormal Myocardial Function," New York, 1917.

‡ Naish and Kennedy, Lancet (Nov. 28, 1914), p. 1242; Butterfield, H. G., Heart, iii (1911–12), p. 203; Cowan, Flemming and Kennedy, Lancet, i (Feb. 3, 1912).

§ Hume, W. and Clegg, S., Quart. Jour. Med.,, viii (Oct., 1914), p. 1; Price F. W. and Mackenzie, I., Heart, iii (1911–12), p. 233.

‖ Rohmer, P., Jahrb. fur Kinderheil., lxxvi (1912).

Little has been written concerning the symptomatology of heart block in children. The patient from which Fig. 131 was taken complained of dyspnea and a sense of fluttering in the heart region on taking sudden exercise—otherwise the child felt well in spite of the fact that his heart never beat faster than 44 to the minute. Distinct paroxysms of unconsciousness (Stokes-Adams disease) seem to be very rare. Hecht* describes a child aged nine years who apparently suffered from typical paroxysms of syncope. The ventricular rate was 40, the auricular 90 to 103.

During the course of an infectious disease attention may be directed to the pulse on account of its slowing down suddenly. This may or may not be accompanied by other symptoms of cardiac embarrassment. Such is the case described by Gosse† in a boy aged 12, who suffered from mitral and aortic regurgitation with adherent pericardium. During a febrile recrudescence of his cardiac condition, heart block developed. Except for the pyrexia there were no symptoms referable to the changed heart rhythm, and myocardial disease would not have been diagnosed without the aid of the polygraph.

Block may occur at any age. Frank and Polak‡ have reported a case of acquired heart block in a child aged two and a half years. The slow pulse here appeared for the first time after the child had had a mild febrile disturbance of unknown origin. The symptoms were mainly dyspnea accompanied by a small weak pulse of 48. The heart was enlarged. Tracings showed that the auricle was beating at the rate of 107 while the ventricle beat at 42.8 to the minute.

That developmental defects in the heart may lead to block has been claimed by several observers. In 1910 Fulton, Judson and Norris§ described a family in which three members showed continuous partial block with slow radial pulse. One of these cases was an infant which at one time presented a systolic murmur which gradually disappeared. Administration of atropin had no effect. The authors concluded that the slow pulse was due to some defect in conduction, possibly a congenital defect in the physiology or anatomy of the bundle or its blood supply. They did not believe the cases due to defects in the interventricular septum.

The case reported by Whipham‖ is the first in which congenital heart block was proved by the electrocardiograph. A child of one and one-half years is described with a pulse of 50. Tracings show typical 2 : 1 block. A loud systolic murmur, together with a radiograph showing a globular heart outline, made the diagnosis of septal defect very probable.

Zahorsky¶ describes a somewhat similar case in an infant 15 months old. In this case the pulse rate varied between 50 and 60, and

* *Loc. cit.*
† Brit. Med. Jour. (June 20, 1914).
‡ Nederland. Tijdschr. voor Geneeskunde (June 10, 1916).
§ Amer. Jour. Med. Sic., cxl (1910).
‖ Brit. Jour. Dis. Child. (Nov. 1915), p. 321.
¶ Interstate Med. Jour., xxii (1915), p. 57.

the symptoms pointed to congenital heart disease (cyanosis, dyspnea, loud systolic murmur). The heart condition one year later was unchanged.

Figure 131 is the electrocardiogram of a boy of 15 who for several years had complained of a sense of precordial uneasiness on exertion. He had never been seriously ill, and had not suffered from any rheumatic symptoms. He was referred from school where a routine examination had revealed the cardiac condition. Physical examination showed a boy mentally and physically about four years behind the normal. The heart was enlarged both to the right and the left. Thrill was absent. There was a rough loud systolic murmur over the precordium, with its maximum intensity over the aortic area. Pulse rate observed at various times over a period of seven months was 40 to 44 per minute. No cyanosis or clubbing were present. The electrocardiogram shows complete heart block.

The diagnosis of heart block and congenital heart lesion here seems justified.*

In order to rule out functional block, atropin may be injected.† In true heart block the pulse rate should not be affected by the drug. In the case described above a hypodermic injection of $\frac{1}{100}$ gr. of atropin sulphate failed to influence the pulse rate in any way as evidenced by an unchanged electrocardiogram before and after its administration.

Note.—The electrocardiograms used as illustrations were kindly taken by Dr. B. S. Oppenheimer of the Electrocardiographic Department of Mount Sinai Hospital.

DISTURBANCES OF THE HEART DUE TO GROWTH

With the improvement in methods of examination of the heart, many cardiac conditions previously loosely spoken of as "functional" have been shown to have a demonstrable organic basis. Among such cardiac conditions are several which are due to an abnormal growth of the heart in comparison to the growth of the body. It is chiefly due to the development of the Roentgen examination of the heart that we have become familiar with these abnormal cardiac types; for they may be recognized by the fluoroscope as presenting definite changes in the size and shape of the heart shadow.

A knowledge of these conditions is important because they occur rather commonly and because they explain to a certain degree at least some of the symptoms so often spoken of as "functional disturbances."

Since these heart symptoms are due in many instances to a disturbance in the relative size of the heart and the body, it is natural that most of them should be found at the time of most rapid bodily development. Such is the case, for the years about the time of puberty is the time when these symptoms become manifest.

* M. H. Bass, Jour. A. M. A., Feb. 2, 1918.
† Hecht, Zeitschr. fur Kinderheil., iv, No. 6.

These cases include not only some of the members of the large group of children showing functional murmurs, but also children the subjects of various forms of constitutional inferiority and asthenia, whose subjective complaints are mainly cardiovascular in nature. Any procedure therefore which will tend to classify and systematize such conditions must be of extreme value, for thereby the question as to whether a cardiac condition is functional in the sense that it is transitory, or organic in the sense that it is permanent and progressive, may be fairly confidently answered. Whether one condemns a child to continued inactivity during a large part of its childhood on the supposition that the complaints of palpitation and dyspnea are coupled with apparent cardiac enlargement, and therefore represent an organic lesion, or whether by fluoroscopy and a radiograph one can assure oneself of the normal size and shape of the heart or the presence of certain well-defined changes in the growth of the heart, will make a vast difference in the handling of the case and in the prognosis.

The Drop Heart

Of particular interest in this respect is the heart described by F. Kraus under the title of "the heart of the narrow chested" (Herz der Engbruestigen) or the drop heart, the characteristic radiographic picture of which has the following appearance (Fig. 132): The heart assumes a median position in the chest, the right and left diameters approaching each other; the shadow assumes a more vertical position, showing that the long axis of the organ approaches the long axis of the body. Instead of resting upon the diaphragm as does the normal heart, the drop heart appears to be suspended from the great vessels and to hang down into the thorax (hence the term drop heart)—an appearance which may be exaggerated by forced inspiration, which, by lowering the level of the diaphragm, causes a further downward and clock-wise movement of the heart apex. When viewed laterally these hearts are seen to lie farther back from the sternum than normally, so that the retrosternal space instead of being gradually obliterated below consists of a vertical band running parallel to the sternum—in other words, the heart's apex and lower border have receded from the sternum. Moreover, probably owing to the lessened apposition of the heart to the diaphragm, the former is abnormally mobile when the body is moved from side to side. As a rule, the middle curve in the left border of the heart silhouette is distinctly exaggerated so that a somewhat mitralized type of shadow results. The drop heart shows on fluoroscopy a strong type of contraction—there is a distinctly large amplitude in the contraction wave and the silhouette reveals particularly prominent pulsations. This is apparently paradoxical since these hearts may be functionally weak, but it can be easily correlated with the overaction shown clinically.

The drop heart may be suspected when in narrow chested, rapidly growing children nearing the age of puberty there is apparent cardiac

weakness, although percussion shows the heart dulness to be abnormally narrow. Such children may complain of palpitation and breathlessness on exertion, and may even present faint murmurs over the precordium. Radiography will reveal the typical narrow drop-like heart shadow.

The occurrence of this type of heart in the narrow chested child at a time of life when certain changes in the relationship of the various portions of the body to one another are taking place is of considerable

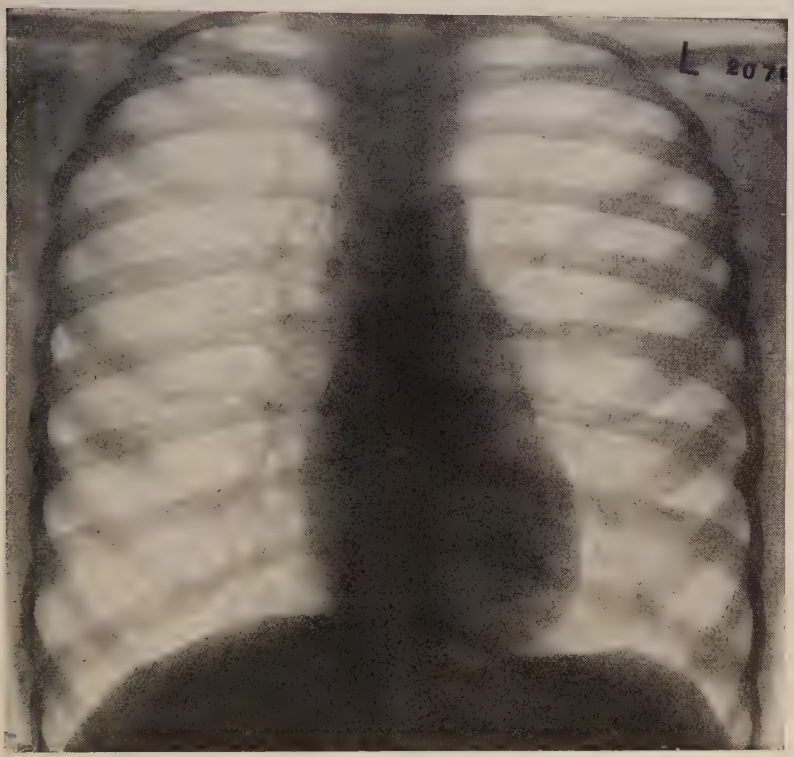

FIG. 132.—Radiogram: Drop heart. Note that the transverse diameter is narrowed and that the long axis of the heart approaches the vertical.

interest. It has been known that in infancy the upper thoracic segment of the trunk is the most prominent, but that as growth proceeds, the lower half of the trunk increases at the expense of the upper. In the so-called narrow chested child, this growth at puberty is excessively rapid, and as a result we obtain an individual of long and narrow stature, with prominent scapulæ, narrow upper abdomen, high narrow liver and a compressed lumbar gutter with resulting depression of the right kidney. In other words, the enteroptotic habitus with its prominent abdomen results. Apparently in these children it is not so much the lengthening of the chest as it is a lengthening of the lumbosacral spine that causes these various anomalies.

These data are especially interesting in the light of phylogenetic development since, as pointed out by Kraus, Widersheim and others, this type of individual is a regressive one, for the long lumbosacral spine with a narrow chest is characteristic of animals in which the horizontal position of the body is found. The assumption of the upright posture, however, has been accompanied by a broadening of the thorax and a shortening of the spine particularly in its lumbosacral portion. Now it is just the failure of these two characteristic changes to manifest themselves to their utmost that results in this regressive narrow chested type of child. This is furthermore emphasized by the studies of Stiller who showed that in many of these individuals the tenth rib, instead of being attached to the ribs above it, was free—the Costa *decima fluctuans*.

We have dwelt at some length on the above conception because it appears to explain not only the anomalous heart silhouette, but because it also gives a more or less potent reason for the functional cardiac insufficiency revealed by these children. We see in such children individuals whose development has been hampered in such a manner that their morphology shows a retrogression to a lower type, and in such cases it does not seem surprising that the functional power of their organs should be below par. Perfect bodily development means not only that each organ should present a perfect type, but that the various organs should be properly balanced and that the correlation between the various parts of the body should be perfect.

The narrow heart is a frequent accompaniment of the phthisical habitus, though whether it stands in any etiological relationship to pulmonary tuberculosis is very doubtful.

It is evident that the drop heart is a product of later childhood, never occurring in infancy or early childhood. This is noteworthy since it is chiefly in these older children that we get the complaints of palpitation, dyspnea and precordial distress which we are apt to term nervous or functional. It is true that many of the asthenic children reveal the drop heart silhouette; but we also find exceptions, both in that we see typical cases of drop hearts in children who have no subjective complaints whatever, and that we see apparently normally built children whose hearts are abnormally narrow. The term drop heart is moreover no hard and fast one; for we can find all grades of narrowness from the exaggerated drop heart to the heart of normal width. In spite of these considerations, however, the conception of a narrow heart as part of a clinical syndrome, is, we believe, a very useful one for which there is at the present time ample proof.

Microcardia

Under this term are included cases in which the measurements of the heart shadow reveal a distinctly small heart. Such children do not show any signs of cardiac weakness, but may have symptoms of a neurotic constitution.*

*Adler and Krehbiel, Arch. Int. Med., ix (1912).

Juvenile Heart

Krehl* has described a type of heart occurring in young individuals in whom symptoms of cardiac hypertrophy are evident without any definite cause such as endocarditis or nephritis. Physical examination reveals signs of left ventricular hypertrophy—the heart dulness is increased to the left, the impulse is heaving, the basic sounds are accentuated. Subjective symptoms, such as dyspnea or palpitation, are complained of, or the patient is unaware of any heart disturbance. To this group of cases Krehl gave the name "Wachstumshypertrophie" (growth hypertrophy) because the enlargement of the heart was considered to be due to the rapid growth of the body. A few years later it was shown by G. Schwartz that these cases have a characteristic fluoroscopic appearance; the heart shadow lies somewhat transversely, the apex is rounded, the pulsations are deliberate and powerful.

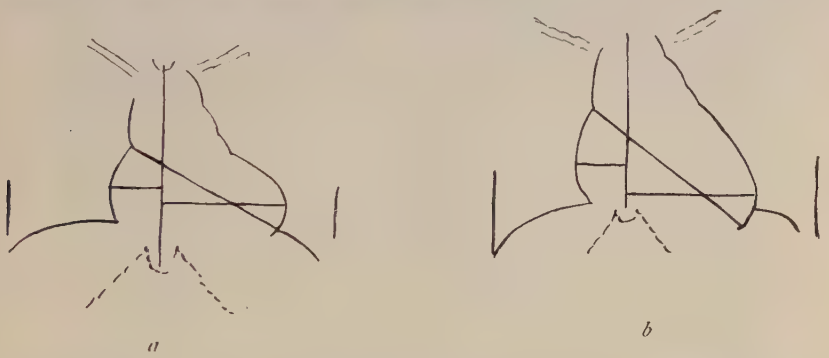

Fig. 133.—(*a*) Orthocardiogram of "juvenile heart." Note transverse position, rounded apex and increased transverse diameter, characteristic of left ventricular hypertrophy. (*b*) Orthocardiogram of normal child's heart for comparison.

We have encountered hearts of this variety in children above the age of nine years, and have described them under the name of the "juvenile heart."† As shown in Fig. 133 the heart silhouette is quite characteristic of left ventricular hypertrophy.

This cardiac condition is probably transitory and its treatment should consist mainly in sparing the heart by restriction of violent exercise.

Closely allied to this group of cases is the condition known as dilatative weakness. By this name Martius designated the cardiac condition of children who after moderated exercise become pale and breathless, with very weak, small and rapid pulse. Physical examination of such cases especially after exertion reveals apparent cardiac dilatation, hence the name "dilatative weakness" (Dilatative Herzschwäche). We have, however, been able to show that the dilatation is only apparent and that no real enlargement of the heart takes place. The condition is found in older children who have grown rapidly.

* Nothnagel's System, xv, p. 391.

† Bass and Wessler, Arch. Int. Med., xi (1913), p. 403.

They show distinct symptoms of cardiac weakness and many are subject to orthostatic albuminuria. Small doses of digitalis are apparently useful.

Miscellaneous Conditions Affecting the Heart

Without being the seat of inflammatory processes, the heart may be affected by a variety of diseases, of which but brief mention need be made here.

In chronic pulmonary disease, especially asthma and emphysema, we may meet with marked cardiac weakness, during which the signs of

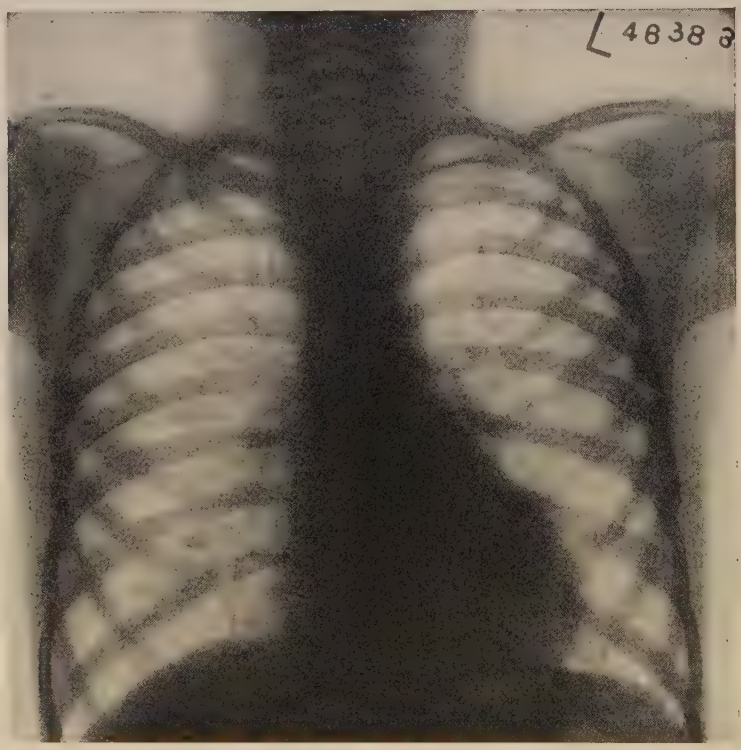

Fig. 134.—Radiogram: Heart in chronic nephritis. Note that the apex is blunt and rounded and that the long axis of the heart approaches the horizontal.

myocardial insufficiency are present. Contrary to what might be expected, the heart is not dilated, but is shown by the Roentgen ray to be long and narrow, being compressed by the overexpanded lung.

In pleural effusion and empyema the heart may be temporarily displaced. In chronic fibrotic pulmonary conditions bands of adhesions may permanently bind down the heart in abnormal positions.

Even in childhood when cardiorenal disease is extremely rare, nephritis may cause distinct cardiac changes.* Hypertrophy of the

* Wessler, Arch. Int. Med., xiv (1914).

left ventricle may take place both in acute and chronic inflammation of the kidney. In Fig. 134 is shown the radiogram of the heart of a child suffering from chronic nephritis. The rounded blunt apex and the transverse position are characteristic. Added to this, is the fact that fluoroscopy shows the heart action to be abnormally deliberate and forcible. The first sound in such cases is loud and booming, the second sound over the aortic area is accentuated, and the apex-impulse is forcible and heaving. Such cardiac changes may or may not be associated with increases in the blood pressure. They are important, since they help to differentiate cases of mild chronic nephritis from the albuminurias so commonly encountered in childhood.

CHAPTER LXXIII

DISEASES OF THE BLOOD-VESSELS

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THE AORTA

Acquired disease of the aorta is rare in childhood. Two main conditions may be briefly considered—aortitis and aneurysm.

Aortitis

Although not a common disorder, quite a number of cases of aortitis are reported in the literature. Only the chronic form of the disease is encountered. It follows many of the infectious diseases (diphtheria, sepsis, scarlet fever, pericarditis), but its most frequent cause is acute rheumatism. Allbutt* has collected the published cases. The chief symptoms consist in continued fever; dull substernal pain which may at times become very severe, resembling angina in its radiation down the left arm; sudden attacks of marked dyspnea suffocative in character occurring mainly at night. A rough systolic murmur may be present over the aortic area, and dilatation of the arch may lead to an area of dulness to the right of the sternum in the second intercostal space.

The site of the lesion is usually in the ascending portion of the arch of the aorta, which loses its elasticity and gradually dilates. Aneurysm may result. Atheroma of the aorta has been found even in very young children, Andral† having seen it in a girl of eight, and Peter‡ in a child of two.

Aneurysm

Aortic aneurysm has been described as occurring in children of all ages. L. de la Rue§ who has collected 14 cases of this disease, finds most of them occurring during the second decade, but a case is described at the age of five months, and several between the ages of three and five years. Congenital aortic aneurism has been reported (Hochsinger). The ascending arch is as a rule involved; also the concavity of the arch and that portion where the ductus arteriosus is given off.

* Diseases of the Arteries, London, ii (1915), p. 143 et seq.
† Clin. Med. (1834).
‡ Union Med. (1890).
§ These des Paris (1903).

A very complete bibliography of aneurism in children may be found in the British Journal of Children's Diseases* in an article by Bronson and Sutherland. These authors classify aneurisms in children according to etiology into the following groups—(1) Arteriosclerotic; (2) traumatic; (3) embolic or septic; (4) false, due to erosion from without; (5) due to congenital anomalies. The most frequent causes are syphilis and aortitis following rheumatism.

The symptoms and the treatment are the same as in adult cases.

PERIPHERAL ARTERIES

Arteriosclerosis, though not a common finding, occurs at all ages of childhood. In congenital syphilis distinct changes have been found in the aorta and peripheral vessels and the spirocheta pallida has been demonstrated in the vascular coats.† In rare instances in infants all the arteries are involved and the smaller vessels may be obliterated‡. As the age of the child increases, the cases become more numerous. Romberg believes that some degree of arteriosclerosis is present in 5.8 per cent. of all the autopsies in children under 15 years of age. The etiological factors here are chiefly various infectious diseases, nephritis being conspicuously absent. The pathological picture has been carefully studied by Wiesel§ who showed that the first change is infiltration of the media and vascuolation of the muscle layer. Later the elastic tissue breaks up and the muscle fibers undergo necrosis. The intima is involved in only a small number of cases.

Apparently most of these cases show no symptoms unless the disease is very pronounced or is located in the aorta. Spontaneous healing seems to be the rule.

Atheroma of the pulmonary artery leads to special symptoms of which marked cyanosis with slight edema and evidence of great hypertrophy of the right ventricle are the most important. Such cases have been reported in a child aged five years,‖ and in one aged 12 years (Rogers). Atheroma of the pulmonary artery may appear as a primary disease or more often may be secondary to chronic bronchitis, emphysema or mitral disease.

In making the diagnosis of juvenile arteriosclerosis one must be careful not to judge simply by the palpability of the superficial vessels, for these are often distinctly rigid when no sclerosis is present. To this condition the name of "pseudosclerosis" has been given. It is a common finding in the neuropathic child (Hamburger). Fischer and Schlayer after pathological examination of a series of such arteries, conclude that "sclerosis of the intima plays no part or a very slight part in the palpability of the vessel. There are changes in the arteries which cause them to appear markedly thickened and which make them

* Vol. xv, pp. 241–358.
† Rebaudi, Monatschr. f. Geburtshuelfe u. Gynaekologie, xxxv (1912), p. 681.
‡ Hale, White and Bryant, Proc. Royal. Med -Chir. Soc. (Jan. 12, 1905).
§ Ztschr. f. Heilk., xlvii (1906).
‖ Veale and Coombs, Brit. Jour. Dis. Child., xii (1915), p. 72.

functionally less competent, without causing any anatomical arteriosclerosis." In these cases there is no increase in the blood pressure.

Children who have these pseudosclerotic arteries are usually high-strung and nervous; they complain of headaches, flushes and palpitation, and faint easily.

Acute disease of the peripheral arteries is rare in childhood. It may be a sequel of infectious disease, especially typhoid, syphilis, pneumonia, influenza and rheumatism; it may follow trauma or result from embolism in the course of cardiac disease. The affected artery may become inflamed with or without a consequent obliteration of its lumen. In the former case, unless rapid collateral circulation is established, gangrene of the parts supplied by the vessel results.

The symptoms in these cases consist of fever, swelling of the affected vessel, severe pain, numbness and tingling along its course, diminution of the vascular pulsation, and if occlusion takes place, dry gangrene.

In the course of measles, spontaneous gangrene of the skin may take place, caused by thrombosis of the smaller vessels.*

Spontaneous gangrene of the extremities is also described.†

In the course of diphtheria, intracardiac thrombosis with resulting embolism, may cause infarcts in the lungs, kidneys, etc., or thrombi lodging in the cerebral vessels may cause monoplegias or hemiplegia.‡

Acute inflammation of the smaller vessels occurs in the bronchopneumonia with measles, pertussis, influenza and when present in the cerebral vessels may give rise to sudden paralyses.§

Aneurysm of peripheral arteries is occasionally met with in childhood. The most common causes are embolism and trauma. Cautley‖ has collected 38 cases in individuals under 20 years of age, 25 of these being under 13 years of age. Males were affected twice as often as females. The location of the aneurisms in this series was as follows: Thoracic aorta 6, abdominal aorta 3, iliac 1, femoral 5, popliteal 2, tibial 4, carotid 3, axillary 2, innominate, coronary, ulnar, dorsalis pedis, and cerebral 1 each. The symptoms and treatment are the same as in adult cases.

Periarteritis nodosa is an exceedingly rare condition in which small nodules form in the course of the small and medium sized arteries. The disease occurs as a rule in adult life, but a case has been reported in an infant of two and a half months (Krzyszkowski), and two in older children, aged respectively 10 and 14 years.¶ The disease is characterized by weakness, emaciation, dropsy and dyspnea, together with symptoms referable to the particular organs affected. It practically invariably leads to a fatal termination.

* Morgenstern and Gruber, Ztschr. f. Kinderh., xii (1914–15).
† v Khautz, Ztschr f. Kinderh., xi (1914).
‡ Leede, Ztschr. f. Kinderh., viii (1913).
§ Poynton, in "Diseases of Children," by Garrod, Batten and Thursfield.
‖ Diseases of Children, London (1910).
¶ W. E. Carnegie Dickson, Jour. Path. and Bact., xii (1908), No. 1.

DISEASES OF THE VEINS

Phlebitis and venous thrombosis are not infrequently encountered in children. As a rule they are due to infectious processes and occur in poorly nourished or marantic children. More rarely they are aseptic and follow mere mechanical compression.

Infectious thrombophlebitis is seen in infants most often in the renal and cerebral veins and cranial sinuses (Finkelstein). The veins in and about the orbit may be involved as an accompaniment of the orbital cellulitis which occurs as a complication of some of the infectious diseases. During the course of otitis media and mastoiditis the lateral sinus and jugular vein may become thrombosed. In such cases blood cultures show the presence of microörganisms in the circulating blood.* As a complication of typhoid fever, thromboses of veins in various parts of the body are described.† Moussous has recorded the cases of an infant 14 months old with bilateral femoral thrombosis following typhoid fever.‡ The symptoms and course of such cases do not differ from those occurring in adult life.

Among the aseptic thromboses those affecting the venæ cavæ are of special interest. Either the superior or inferior cava may become involved, or both vessels may become simultaneously affected.§ In such cases dyspnea and anasarca lead to the diagnosis of nephritis, but the urine shows little or no renal involvement. A case of this character is described by J. L. Roberts‖ in a boy aged five years in whom thrombosis of both cavæ resulted from compression due to a mass of mediastinal nodes.

Phlegmasia alba dolens is described, especially by French clinicians as occurring in the course of pulmonary tuberculosis and chlorosis.¶

* Libman and Celler, Am. Jour. Med. Sc., cxxxviii (Sept., 1909).
† Veseaux de Lavergne, Paris Thesis, 1903
‡ La Pratique des Maladies des Enfants, Paris, iv (1911).
§ A. Meyer, Mount Sinai Hosp. Reports (1903).
‖ Lancet (Nov. 7, 1903).
¶ T. Salle, Paris Thesis (1903).

CHAPTER LXXIV

PHYSIOLOGY OF THE BLOOD

By William Palmer Lucas, M.D., and E. C. Fleischner, M.D.

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BLOOD-FORMING TISSUES

In the embryo, active blood-forming tissues have been found in various organs—the liver, spleen and lymphatic tissue—but at birth the blood-forming tissue is limited mainly to the red bone marrow, though the spleen and to a less extent the lymphatic tissue may continue for a few months to form red blood cells. The red bone marrow at birth fills the long bones as well as the flat bones and the small spongy bones. From infancy on, however, there is a gradual deposition of this red bone marrow in the shafts of the long bones by a fatty, gelatinous marrow which does not, under normal conditions, produce red blood cells, leaving the functionating marrow to the ends of the long bones, the flat bones and the small spongy bones by the time adolescence (15 years) is reached. This fatty marrow, however, under abnormal conditions may take on its embryonic activity and produce red cells, though they are always of an abnormal type. Under great pressure, in certain anemias the spleen may take on its early function of producing red blood cells. It is very doubtful whether, under very great pressure, the lymphatic system can be brought to do this; and it is doubtful whether the liver ever takes on this function after embryonic life.

The presence of hemoblastic tissue always indicates the power to form red cells, and wherever found it is a single and similar tissue. In the bone marrow, which is the most typical red blood forming organ, this tissue is composed of a fine reticular mesh work with wide endothelial walled blood-vessels called sinusoids. It is a debated point whether these sinusoids have an intact endothelial wall. It is probably true that during infancy and early childhood the sinusoids have a more or less free communication with the blood-forming islets, but as normal growth progresses these sinusoidal spaces become intact. Leading into these sinusoids, in which the circulation is very slow, are small vessels supplied with vasomotor nerves.*

The reticulum outside the sinusoids has a very delicate structure, and enmeshed in this reticulum are found all the differently formed elements of the blood.

The most primitive cell found in the bone marrow is a large mononuclear cell with an irregular form and a large nucleus. The proto-

* Drinker, et al, Jour. Exper. Med., xxviii (1918), pp. 249–383 and Amer. Jour. Physiol., xl (1916), p. 514.

plasm of the cell stains a deeper blue with Wright's stain than does the nucleus. These cells are the most primitive form of bone marrow cells; from them originate probably all the other cells produced in the bone marrow. Only occasionally are they found in the circulating blood; under such conditions they are often mistaken for myelocytes or large lymphocytes. Their presence is not considered a good prognostic indication as it denotes a very marked stimulation of the bone marrow and indicates that the bone marrow is being forced to the extreme limit in its production of cells.

Nucleated red cells are present in the bone marrow in great abundance. They are found normally in the fetal circulation and may be quite abundant in the first few hours after birth. They disappear rapidly from the circulation of the newborn and are not found normally after the first week and seldom after the third or fourth day.

Normoblasts are the chief type of nucleated red cells and are approximately the same size as the ordinary red blood cell. They are round, with a fine reticulum holding the protoplasm and hemoglobin. Their nuclei are about 4 microns in diameter.

Megaloblasts are much larger than normoblasts, often attaining a size of 20 microns and containing nuclei 10 microns in diameter. A nucleated red cell with a diameter of 8 microns may be classed as a megaloblast. Then uclear chromatin is more widely separated, so that the nucleus does not take as deep a stain as the normoblast nucleus. Polychromasia is more often found in megaloblasts than in normoblasts, and is more common in nucleated than in non-nucleated red blood cells.

Occasionally nucleated cells or microcytes are present which are considerably smaller than the normoblasts. Intermediate types of cells between the normoblasts and megaloblasts, both as to size and staining properties, may be found. All types of nucleated cells are found in the bone marrow, though the normoblasts far outnumber the megaloblasts under normal conditions. Under pathological conditions, however, there may be so rapid a proliferation of the megaloblasts in the bone marrow that they outnumber the normoblasts. Their presence in greater number in the circulation indicates bone marrow involvement.

The red cells are surrounded by a fine membrane, inside of which the hemoglobin is held in a scanty reticulum; this membrane ruptures very easily. Under normal conditions, the red cells take acid dyes much more readily than basic stains. In certain pathological conditions, however, the affinity for basic dyes may be markedly increased. This condition is known as polychromatophilia or polychromasia. In fetal blood, as well as in certain anemias, a diffuse polychromatophila is found. This diffuse polychromatophilia is to be regarded as a stage in the formation of hemoglobin and is therefore a regenerative process.

Another type of polychromatophilia found especially in the grave anemias is the granular or punctate basophilia. The granules may

be few or many. This condition is usually found in association with nucleated red blood cells. These granules are also found in the bone marrow of fetal and newborn infants. The process is spoken of as "stippling" and is generally considered as representing nuclear fragments.

Besides these nuclear particles, there is in certain conditions an increase in the reticular substance. This is a sign of blood regeneration and is found after hemorrhages and in certain anemias. It is present normally in from about 0.8 to 2.0 per cent. of red blood cells. The presence of this irregular basophilic staining is important in the study of pathological bloods.

The appearance of nucleated cells, polychromatophilia, reticulation and probably stippling is to be taken as a sign of blood regeneration, showing the presence of younger forms of red blood cells than the normal erythrocytes. At the present time, the connection between reticulation and stippling seems to be regarded as closer than that of reticulation and polychromatophilia. These types are found clinically in a variety of blood conditions.

Reticulation is found very constantly in pernicious anemia, both before and after transfusion* and has also been shown before and after splenectomy by Lee and Vincent.† Robertson and Bock,‡ think that the percentage of reticulated cells has a definite prognostic value in cases of traumatic hemorrhage. These cells are increased when there are signs of blood regeneration; i.e., when the blood-forming organs are stimulated to keep pace with the destruction. They are diminished in plethoric conditions; *i.e.*, when the bone marrow is not being stimulated and there is an excess of red cells in circulation, so that there is no need for increased activity of the bone marrow.

The present concensus of opinion is "that reticulation is an evidence of blood regeneration and the percentage of these cells in the blood stream is a reliable indication of the hematopoietic activity of the blood-forming organs."§

The technique of staining the reticulation and making permanent preparations is given by Cunningham as follows:

"The technique is divided into two stages. First, a small drop of a 0.3 or 0.5 per cent. aqueous or alcoholic solution of brilliant cresyl blue is placed on the end of a clean slide or the center of a cover glass, smeared around over an area 1.5 cm. in diameter with the aid of a match or glass rod and permitted to dry. After this is dry, there may be a narrow margin of thick stain which should be wiped off with a damp cloth, leaving a central uniform area. These slides or cover glasses may be prepared in large quantities, and if stacked side by side in a box and kept dry the stain will not deteriorate. The second stage consists of taking a drop of fresh blood on a clean coverslip and

* Vogel, K. M., and McCurdy, U. F., Arch. Int. Med., xii (Dec., 1913), p. 707.

† Lee, R. I., Minot, G. R., and Vincent, B., Jour. A. M. A., lxvii (1916), p. 719.

‡ Robertson, O. H., and Bock, A. V., Report of Shock Committee, Medical Research Committee; No. 25 (March 14, 1919), p. 222.

§ Arch. Int. Med., xxvi (Oct., 1920), p. 407,

dropping it face down on one of the areas of dried stain. If the coverslip is clean, the blood will quickly spread to the edges. The stain goes into solution almost instantly. (This preparation may be observed as a vital stain.) The cover glasses or slide and cover glass are now pulled apart as in making an ordinary blood smear and are permitted to dry. Smears may also be made by placing the drop of blood directly on the dried stain and spreading it with a cigarette paper or another slide. On drying, the blood turns a dirty greenish blue color. The slide or cover glass is then stained with Wright's blood stain. Too vigorous washing causes the reticulum to lose some of its stain. The preparation is dried in the usual manner and when mounted in Canada balsam keeps at least four months and probably much longer.

"The reticulum is stained a deep or light blue, depending on its density, and gives a striking picture in contrast with the pink protoplasm of the cell. Various types of reticulation are easily seen from the heavy skein-like material to knotted granular particles connected by delicate blue threads and finally the separate granules which resemble stippling seen with Wright's stain alone. The nucleated erythrocytes in human blood usually have many fine threadlike blue staining filaments around, or radiating from the nucleus. There is no polychromatophilia seen. Whether the reticulation has replaced the polychromatophilia or not is a question requiring further investigation. The examination of many smears certainly suggests this as a possibility."

Megaloblasts are the progenitors of the megalocytes, the normoblasts of the erythrocytes, and the microblasts of the microcytes.

The erythrocytes are the normal oxygen carrying cells of the blood, due to the fact that they are the only cells that carry hemoglobin which is the essential oxygen carrying substance in the blood. Upon hemoglobin depends the presence of oxygen as it is needed, and under normal conditions the amounts needed are furnished. It is certain that its diminution is capable of producing diseased conditions and especially so in the anemias, both primary and secondary.

Barcroft,* in his studies on the respiratory function of the blood, points out that, "In warm-blooded animals, muscle, when worked at its full power uses up its own volume of oxygen in about 10 minutes. This oxygen is carried to it by the hemoglobin of the blood, a substance so rich in oxygen that a relatively small quantity of blood satisfies the need of the muscle. Were it not for this pigment, some 200 c.c. of fluid would have to be circulated through every gram of muscle in 10 minutes of time. To put the matter in another way, blood carries about 40 times as much oxygen as the same volume of plasma. Therefore, to convey as much oxygen around the body as is carried by the blood would, in the absence of hemoglobin, demand 150 kg. of plasma, or perhaps more. The contents of the vascular system would therefore amount to twice the present weight of the body. The body would, in short, be unable to cope with the weight of its own blood.

* "The Respiratory Function of the Blood," Cambridge University Press (1914).

The whole basis of its economy, therefore, hinges upon the accidental possibility of the occurrences and properties of hemoglobin."

Barcroft points out that any disturbance which interferes with the oxygen-carrying ability of the red cells must have far reaching results. These results, *i.e.*, the loss or diminution of hemoglobin or the interference in its function in any way, are generally grouped amongst the anemias. It is not to be assumed that anemias are not also due to interference in the production of red blood cells. The carrying of oxygen by the cells depends upon a number of different factors—the age of the cells and the condition in which they are extruded from the blood forming organs. These and probably other factors less well understood undoubtedly play a part in the amount of oxygen which the cells are capable of carrying.

Hemoglobin may be present in quantitatively sufficient amounts and yet the oxygen be unable to be carried or given off in sufficient amounts to satisfy the needs of the tissue cells throughout the body. The simplest example of this inability to give off oxygen, even though hemoglobin is present in normal amounts, is produced by simple cold. Another example is the presence of abnormal salt concentrations of the plasma. Exactly how these two factors of temperature and general salt contents of the plasma affect the affinity of hemoglobin for oxygen is not well known. Barcroft has shown that the ability to absorb oxygen, i.e., the saturation of hemoglobin, is affected by temperature; for instance, at 16°C. the percentage of saturation is 92, whereas at 49°C. it is only 6. Barcroft also shows that the same condition holds at a much higher oxygen pressure; at a temperature of 16°C. the percentage of saturation was 96, whereas at 38°C. it was 52.

Barcroft points out also that "at 18°C. 35 minutes were required for the reduction of hemoglobin from 100 per cent. to 94 per cent. saturation; at 38°C. it required only 7.5 minutes to reduce it from 94 per cent. to 77 per cent."

On the other hand, the dilution of the blood has no effect upon its oxygen capacity. Barcroft gives Burns' figures on this point, as follows:

Degree of dilution of blood	Oxygen capacity by absorption method, per cent.	Oxygen capacity by ferricyanide method, per cent.
Undiluted	17.6	17.4
5 times	17.6	17.5
7 times	17.8	17.1

From such experiments it is clear that the amount of oxygen that can be taken up and the rapidity with which oxygen can be given up, varies with the temperature of the body. Temperature regulation, therefore, during early infancy, assumes a new importance in relation

to the ability of hemoglobin to combine with oxygen, and undoubtedly explains acidosis occurring during low temperatures in the newborn and in delicate infants and also the cyanosis which occurs in these infants with low body temperature.

The fact that hemoglobin is a colloid and the knowledge we have of the inter-relation between electrolytes and colloids make it evident that the salt contents of the blood must affect and regulate to a certain extent the transfer of oxygen. It has been shown that potassium salts are capable of causing hemoglobin to absorb oxygen to some degree. Many studies have demonstrated the fact that the loss of water, with the resulting concentration of the salts, affects the oxidation of the body. The buffer quality of these salts undoubtedly affects the oxygen transferred from the hemoglobin to the cells. This is, as we know, intimately connected also with another factor; i.e., the hydrogen ion concentration of the blood. It is well known that increasing the acidity of the blood lessens its active concentration of oxygen. An increased acidity of only one part in each hundred million affects immeasureably the concentration of free carbonic acid, and in this way affects directly the ability of hemoglobin to unite with oxygen. The importance of studying the relation of hemoglobin to these three factors—temperature, electrolytes, and hydrogen ion concentration—is indicated in the study of almost all blood diseases.

Harrop* has lately correlated the oxygen consumption of erythrocytes with the enumeration of reticulated cells. His results are as follows:

"1. Normal mature human erythrocytes have no oxygen consumption measurable by present methods.

"2. Where it is measurably increased in the blood of individuals with anemia, the oxygen consumption has no relation to the severity of the anemia and no constant relation to histologic abnormalities in the erythrocytes other than increases in the number of reticulated cells.

"3. Blood which contains abnormal numbers of reticulated erythrocytes has an oxygen consumption proportional to the percentage of reticulated cells present.

"4. The data afford evidence that the two phenomena go hand in hand. Both are due to the presence of abnormal numbers of youthful cells, and both are probably rather accurate indicators of functional variations in the bone-marrow and of the amount of blood regeneration."

There has been much discussion as to the origin of hemoglobin. The mitochondria present in the earliest red cells is supposed to be concerned in the formation of hemoglobin. As the mitochondria represents a period in the life of the cell before the reticulum is formed, it seems that it may be the probable source of hemoglobin; at least there are no definite facts to disprove this theory. Whether mitochondria itself is transformed into hemoglobin has not been definitely

* Arch. Int. Med., 23 (1919), p. 745.

proved at the present time; it is certain, however, that after the red cell has obtained its full growth and arrived at the stage of the erythrocyte it is no longer able to form hemoglobin. This is important from the point of view of treatment which will be referred to later; but it is evident that drugs such as iron could have no effect on the cells already in circulation. Therefore, after therapy is started, the new cells forming in the bone marrow are affected and not the old cells in circulation.

The fragility of red blood corpuscles has received considerable study. The ease with which hemoglobin escapes from red blood cells in circulation is important in considering a number of pathological conditions. The escape of hemoglobin may be due to an altered state in the blood cell itself or to diminished fragility. The resistance of the red blood cells to various concentrations of salt solutions varies in different conditions. This can be applied as a simple test in the study of the red blood cells.

Butler* gives the following technique:

"Kahlbaum's pure sodium chlorid has been used in making up all solutions, and all solutions have been renewed daily. Three solutions were made up to commence with:

"A 1 per cent. solution of sodium chlorid (100 c.c.).

"A 0.85 per cent. solution of sodium chlorid (100 c.c.).

"A mixture of 0.85 per cent. sodium chlorid and 0.85 per cent. sodium citrate (100 c.c.).

"In order to prepare the desired dilutions of saline solution, the following procedure is carried out:

"Two well calibrated burettes are taken and washed with the solution which they are to contain, one is filled with the 1 per cent. solution of sodium chlorid and the other with distilled water. Examples of the method of obtaining the dilutions are given:

"To prepare a 0.3 per cent. NaCl solution, mix 3 c.c. of 1 per cent. NaCl with 7 c.c. of distilled water.

"To prepare a 0.325 per cent. NaCl solution, mix 3.25 c.c. of 1 per cent. NaCl with 6.75 c.c. of distilled water.

"To prepare a 0.35 per cent. NaCl solution, mix 3.5 c.c. of 1 per cent. NaCl with 6.5 c.c. of distilled water.

"To prepare a 0.375 per cent. NaCl solution, mix 3.75 c.c. of 1 per cent. NaCl with 6.25 c.c. of distilled water.

"To prepare a 0.4 per cent. NaCl solution, mix 4 c.c. of 1 per cent. NaCl with 6 c.c. of distilled water.

"The solutions are allowed to run from the burettes and mix in small glass bottles which possess air-tight stoppers. We are thus provided with 10 c.c. of freshly prepared solutions of sodium chlorid of different strengths in well-stoppered bottles, upon each of which can be marked the strength of the salt solution it contains.

"For the actual experiment capillary pipettes are made, but with a finer bore than those described by Wright. The broad end of

* Butler, G. G., Quart. Jour. Med., vi (1912–13), p. 145.

the capillary pipette is fitted with a rubber teat, and at a convenient distance from the end of the capillary portion a fine transverse line is marked with a glass writing pencil: The portion thus marked off is conveniently about two-thirds of an inch in length, and represents the unit standard of volume on which the experiment is to be performed. One of the bottles of standardized salt is then taken and a series of nine columns of the fluid is withdrawn from it into a capillary pipette, each column corresponding accurately in length to the unit marked on the pipette, and each column separated from the next by a bubble of air. These columns of fluid and air bubbles are drawn into the wide neck of the capillary pipette, where they mix, and the air bubbles got rid of; a continuous column of salt solution, representing the nine columns combined, may now be driven down the capillary portion and its length marked on the pipette. This done, the saline solution is blown into a miniature test-tube made from glass tubing ¼ inch in bore and 1½ inches in length, sealed at one end by being drawn out in a flame so as to form a slightly tapering extremity. The process of measuring the nine volumes of each other solution can now be carried out rapidly and easily, for this amount is marked on the capillary pipette. It is scarcely necessary to note that the capillary pipette is washed with a little of the saline to be used in order to remove any of the previous saline solution that may be clinging to the pipette. A series of small tubes is thus set up, each containing nine volumes of salt solution of known strength. The thumb of the patient is cleaned and then encircled at its base with an elastic band to cause engorgement. By pricking the thumb close to the nail-bed with a surgical needle a good flow of blood is obtained, and a series of columns of blood may now be drawn up into the capillary pipette, each column of blood being accurately measured by the unit standard of volume marked on the pipette. The first two columns of blood drawn up are not used in the experiment, for they are contaminated with the remains of the salt solution left in the capillary pipette. The requisite number of columns are taken into the pipette and then one column is injected into each of the miniature test-tubes. Gentle shaking at once mixes the blood with the saline solution. The miniature test-tubes are then placed aside for a short time in order to allow the mixture they contain to settle down before observations on the extent of hemolysis are recorded. If necessary, gentle centrifugalizing will complete the sedimentation. It should be noted that in the experiment so performed there is a constant dilution of blood to the extent of 1 in 10.

"The most likely source of error occurs at the stage of measuring nine small volumes of saline solution. However, this is only performed once in the examination of any blood, so that the error, if it occurs, is a constant one and identical for each dilution of saline solution. This, I think, compares favorably with the other methods where for every dilution of saline solution used there is a source of error, and probably a very variable one.

"The estimation of the extent of the hemolysis in the experiments has been made entirely by the depth of tints, and the following terms have been employed:

"Complete hemolysis—when no red deposit is observable.

"Marked hemolysis—when the red tint is marked and yet there is a red deposit of cells remaining.

"Distinct hemolysis and trace of hemolysis applying to less deep tints."

The conclusions which he feels justified in making are:

"1. The minimum resistance of the normal red blood corpuscle when examined as blood is shown as commencing hemolysis in 0.375 per cent. to 0.4 per cent. sodium chlorid solution when a 1 in 10 dilution is used. The resistance of washed red corpuscles is normally less than that of unwashed corpuscle, the minimal resistance being obtained in a salt solution of 0.425 per cent. to 0.45 per cent. sodium chlorid solution.

"2. The necessity of employing a constant dilution of blood in recording results in order that they may be comparable has been demonstrated, and the lack of this precaution is the cause of the discordant results of other observers.

"3. The rapidity with which washed red corpuscles in normal saline alter their resistance has been shown, and the necessity of experiments being conducted with freshly-washed red corpuscles has been pointed out. Such deterioration is not demonstrable in red corpuscles kept in citrated plasma for 24 to 48 hours.

"4. Different anti-coagulants may be used, except leech extract, without altering the red corpuscle fragility, provided the red corpuscles are subsequently washed with normal saline solution.

"5. Oxygen is capable of decreasing the fragility of the red blood corpuscle. Carbon dioxide has a very marked effect in increasing the fragility, and these two effects are interchangeable.

"6. The decreased fragility of the red corpuscles in obstructive jaundiced conditions has been confirmed.

"7. The increased fragility of the red corpuscles in congenital acholuric jaundice is confirmed. The effect of oxygen and carbon dioxide on these corpuscles has been shown not to differ from the effect on normal corpuscles.

"8. A slightly decreased fragility of the red corpuscles has been demonstrated in pyemia, septicemia, pneumonia, and chronic tubal nephritis.

"9. An increased fragility is shown in cyanosed states.

"10. Fragility appears to be normal in erysipelas, scarlet fever, Grave's disease, carcinoma, syphilis, general paralysis, tabes, chlorosis, pernicious anemia, myelemia, lymphemia, purpura, paroxysmal hemoglobinuria and malaria.

"11. The fragility of the red corpuscles in diabetes appears to vary considerably.

"12. The effect of ingestion of sodium chlorid has been noticed to decrease the fragility of red corpuscles."

In any study on the regeneration of hemoglobin and red cells it is important that the determination of hemoglobin percentage be as accurate as possible. At the present time there is so much variation in the different methods in use that many of the older recorded estimates must be entirely disregarded.

The ordinary Sahli method, which is perhaps most commonly in use, gives inaccurate results because the standard color tubes when checked against the oxygen capacity method of Van Slyke* show great variation in color density. It has been found that as these standard tubes fade their error varies from 5 per cent. to 29 per cent. Sahli found that the artificial color standards were not satisfactory and developed the acid hematin method; hemoglobin is converted into acid hematin by the addition of 0.1 n HCL and then compared with a standard of like material. Palmer† showed that this standard was not permanent and that there was considerable delay in maximum color development. Newcomer‡ compared the hematin suspension of blood with a piece of brown colored glass of definite thickness. The method is based on spectral photometric data. The comparison is made with the Duboscq colorimeter.

In 1892, Hoppe-Seyler§ published a procedure for the accurate determination of hemoglobin in the form of carbon monoxide of hemoglobin. Haldane‖ simplified this method by using Gower's instrument.

In 1918, Palmer¶ published a method which is undoubtedly the most accurate method we have of determining hemoglobin per cent. and the oxygen capacity of the hemoglobin. The principle is that of Hoppe-Seyler's procedure, making a comparison of carbon monoxide hemoglobin solution with a standard of known hemoglobin content. Ammonia solution is used as a diluent instead of water. The color comparison is made with the Duboscq colorimeter. We have been using with great satisfaction this method slightly modified by Robscheit.**

Robscheit determines the hemoglobin in the form of acid hematin, employing Palmer's method of standardization. The oxygen capacity of a sample of dog's blood is determined by Van Slyke's method and the hemoglobin content computed. An acid hematin standard in the form of a 20 per cent. suspension of red blood cells is made up. A 1 per cent. dilution from this suspension is made so that it will read 100 per cent. hemoglobin. The time element for allowing the maximum color of acid hematin to develop plays a very important role. The standard, after preparation and dilution, is allowed to stand 24 hours

* Van Slyke, D. D., Jour. Biol. Chem., xxxiii (1918), p. 127.
† Palmer, W. W., Jour. Biol. Chem., xxxiii (1918), p. 119.
‡ Newcomer, H. S., Jour. Biol. Chem., xxxvii (1919), p. 465.
§ Hoppe-Seyler, F., Z. physiol. Chem., xvi (1891–92), p. 505.
‖ Haldane, J., Jour. Physiol., xxv (1899–1900), p. 295; xxvi (1900–1901), p. 497. Haldane, J., and Smith, J. L., Jour. Physiol., xxv (1899–1900), p. 331.
¶ Palmer, W. W., Jour. Biol. Chem., xxxiii (1918), p. 119.
** Robscheit, F. S., Jour. Biol. Chem., xli (1920), p. 209.

to insure correct readings. A 1 per cent. dilution of the suspension is employed for direct color comparison. The same time factor is used for the blood to be tested. A 1 per cent. solution of blood is used for the determination of hemoglobin. A 0.1 n HCl is employed throughout the procedure for the original standard suspension as well as for all further dilutions. The entire amount of diluent is used at once: i.e., 1 c.c. of the packed red cells is discharged into the volumetric flask containing 50 c.c. of 0.1 n HCl, then mixed, and the volume made up to 100 c.c. with 0.1 n HCl. The suspension is then allowed to stand 24 hours in the ice chest, is thoroughly shaken again, for it must be remembered that this is a supension and not a solution, and then read. This method of hemoglobin determination is like Palmer's and the readings are almost identical when compared with his method.

The source of light used for color comparison makes little difference. Light from a northern exposure or that from a nitrogen-filled bulb filtered through "Daylite" glass gives equally good readings. The slight turbidity in the hematin 1 per cent. solution does not interfere with accurate color comparison.

On prolonged standing, some of the hematin settles to the bottom of the flask or container, but when the mixture is thoroughly shaken again the readings obtained are unchanged. It is very essential that all acid hematin suspensions, whether concentrated or diluted, are thoroughly mixed before any readings are made.

Neither the concentrated solution nor the 1 per cent. solution loses strength by keeping over long periods. If the 1 per cent. solution is made up from the 20 per cent. stock solution once a month and is kept in the ice chest with a fairly constant temperature, 1° to 4°C. fluctuation, the standard keeps for an indefinite period. For clinical use, the 1 per cent. standard is put into one of the Sahli tubes and the blood to be tested is diluted with 0.1 n HCl to the point where the colors match. This is allowed to stand for an hour and then read.

Robscheit's method of preparing the blood for hemoglobin determination in the form of acid hematin is slightly simpler than the carbon monoxide method, for the former makes unnecessary the extra step of saturation with carbon monoxide. The slight disadvantage in this method is the time interval necessary for the maximum color of acid hematin to develop; but in favor of the acid hematin solution are the advantages that it keeps for a longer period than the Palmer method and the color is easier to match than the red tint. For hospital practice, the acid hematin standard can be kept unchanged for at least eight months, and the 1 per cent. solution may be prepared from time to time from the standard concentrated solution. This 1 per cent. solution is put in the standard tube of the common Sahli hemoglobinometer. This insures an accurate base line for hemoglobin determination and by refilling the Sahli tubes once a month will give accurate clinical determinations. Under present clinical methods such results, as pointed out, have not been the rule and these are much to be desired in the study of blood regeneration or destruction.

The number of red cells varies more during infancy and childhood than during adult life, due to the instability or immaturity of the blood-forming organs. During the first week of life the number of red cells is increased; often as high a count as seven or eight million may occur. This is followed by a marked drop by the end of the second week, and the number remains below the normal five million count during all of infancy and most of childhood. This first increase is undoubtedly due to an increased blood volume as it was found in newborn infants that the blood volume averaged 14.7 per cent. as against the normal average for older children of 10.9 per cent.

During the first day or two, nucleated red cells may be found in the circulation; after the first week they usually disappear. During the period of increased red cells, there is also found a high hemoglobin percentage. This is often as high as 120 per cent.; sometimes even a higher percentage is present for a few days. During this time there is also a higher specific gravity average 1.070 as against 1.050, which is the normal average in adult life.

Certain physiological conditions also have a direct bearing upon the number of red cells found in the circulation. The polycythemia found in high altitudes is well recognized, and, as has been shown, this depends also on variations in the blood volume. In this condition not only is the number of red cells changed but also their size, as there is a tendency to smaller cells than the normal. This tendency is interpreted as an alteration in the activity of the bone marrow. It has been shown, however, that the hemoglobin total percentage is not increased. The oxygen capacity is lowered. Cold affects the number of red cells found in the peripheral circulation by causing a localized stasis, so that in making blood counts it is important to consider the effect of temperature.

Conditions which raise the concentration of the blood, such as vomiting, diarrhea, profuse sweating, or polyuria may produce an increase in the red cells. These conditions produce a water loss in the blood so that the hematocrit reading would show a marked reduction in the normal plasma and an increase in the cell content. We have seen the cell content as high as 80 per cent. and the plasma content as low as 20 per cent. in cases of acute diarrhea. Marriott* has reported the same findings in acute diarrhea and vomiting. It is therefore important in interpreting the number of red cells to consider the change in blood volume and water content of the body.

Weigert† shows that there are two factors—age and feeding—which determine the water content of the body. The effect of food on the water content and therefore the concentration of the blood has been shown to have a definite relationship to the amount of carbohydrate food given. With a high carbohydrate food there is a definite retention of water in the tissues. It has been shown that glycogen when it is stored in the body takes with it three times its weight of water,

* Marriott, W. McK., Amer. Jour. Dis. Child., xx (Dec., 1920), p. 461.

† Weigert, R., Jahrb. f. Kinderh. lxi (1905), p. 179.

so that children on a high carbohydrate diet would tend to have a diminished blood volume.

Utheim,* however, shows that not all children suffering from carbohydrate disturbances (athrepsia) showed a diminished blood volume in proportion to the body weight. He found that there was a marked difference in the venous and capillary blood with a higher red blood cell count and hemoglobin content in the capillaries. This is due to the peripheral constriction of the blood-vessels which is not found in normal infants nor in infants suffering from other disease except acute diarrhea. In these athreptic cases, however, the hematocrit readings gave a low cell percentage as compared with the high plasma percentage.

The rate of the blood flow, as pointed out by Utheim, is one of the most important physiological factors to be considered. In diarrhea and athrepsia the blood flow was decreased very markedly. In athrepsia the flow was at times as low as 1, 2, 3, 4 to 12 or 13 c.c. per 100 gm. of arm per minute, and in acute diarrhea it was as low as 3, 5, 8, 10 or 12 c.c. per 100 gm. of arm per minute as compared with 17 c.c. which Utheim takes as the normal flow for infants; whereas in anemia he found it varied from 27 to 32 c.c. per 100 gm. of arm per minute.

Of course there are other factors than the viscosity of the blood and the total blood volume to be considered in estimating the rate of blood flow, such as the condition of the heart and the influence of the vasomotor system. In cases of acute diarrhea, starvation or athrepsia, as soon as food or fluid is given the blood volume will in most cases be rapidly restored as well as the blood flow increased.

In congenital heart disease there is often a marked increase in the number of red cells. This is especially true in cases with cyanosis due to the stimulation of the bone marrow by the increased CO_2. In certain toxic conditions, such as coal-gas poisoning, benzine poisoning and occasionally in diabetes, there is an increase in the methemoglobin or carbon dioxide circulating in the blood. In these conditions an increased stimulation of the bone marrow occurs with a resulting increased number of red cells in the peripheral circulation. True congenital polycythemia is an entirely different condition and will be discussed later.

The second formed element that appears in the blood is the leukocyte. As seen in fresh specimens it is a highly refractile, colorless cell with characteristic nucleus and protoplasm. The size of the nucleus varies, as does the character of the protoplasm in the different types of leucocytes.

The granular leucocytes have their origin in the bone marrow tissue; though they may, as has also been said concerning erythrocytes, be formed wherever there is the essential blood forming tissue whether that be in the spleen or in the liver, as in the embryo. The origin of the granular leukocytes is probably the same as that of the hemoglobin containing cells. As far as our knowledge goes at the present time,

* Utheim, K., Amer. Jour. Dis. Child., xx (Nov., 1920), p. 366.

the earliest cell in the bone marrow may produce either hemoglobin carrying cells or the granular leukocytes. In severe pathological conditions it is at times impossible to differentiate certain cells as to whether they belong to the hemoglobin containing group or to the granular leukocytes. If myelocytes predominate, we classify them as the parent cell of the granular leukocyte; if, on the other hand, megaloblasts or normoblasts predominate, we classify them as belonging to the hemoglobin bearing cells. These undifferentiated cells known as hemoblasts rarely appear in the circulating blood except when the bone marrow has been pushed to the limit in its function of producing cells. They are often spoken of as premyelocytes or premyeloblasts. It might be better, however, to consider them as the earliest type of cell and classify them as hemoblasts.

In the first stage of differentiation the granular leukocytes are myelocytes. These myelocytes may be neutrophilic, basophilic, or eosinophilic myelocytes, depending on the staining properties of their granules and the size of their granules. In all these cells, the nucleus is large, round, or oval and stains a light blue with Wright's stain. The neutrophilic myelocytes are the most numerous and are more likely to appear in the circulation than are either the basophilic or the eosinophilic myelocytes.

The basophilic myelocytes may have large, irregularly shaped granules with an irregularly shaped nucleus; or they may have very fine granules with either a single nucleus or with a polymorphonuclear variety. The latter variety of cell is formed not only in the bone marrow but also in the lymph glands and is more commonly found in the circulating blood than the basophilic myelocytes with large nuclei.

The eosinophilic myelocytes have granules with an affinity for acid stains. There has been a great deal of discussion in regard to their granular material. The question has been much debated as to whether their granulations are derived from the breaking down of red blood cells, thus being really hemoglobin containing particles, or whether they are obtained through the degeneration of muscle tissue. We know that under certain stimuli these eosinophilic cells appear in great numbers in the blood. What the affinity is we do not know. We do know that all types of myelocytes are gradually transformed into polymorphonuclear granular cells. The only thing that is constant is that the types of granules do not change; basophilic myelocytes produce basophilic polymorphonuclear cells; neurophilic myelocytes produce the most common form, the polymorphonuclear neutrophile; and the eosinophilic myelocytes produce the polymorphonuclear eosinophile. We know that the ordinary response is first met by the polymorphonuclear neutrophil; that certain toxins, such as intestinal parasites, call for a large number of eosinphilic cells; and in certain pathological conditions, as in myelogenous leukemia, we get a great increase in the large basophilic granular cells.

The final age of these granular cells is determined by the number of lobulations found; as a rule, the older the cell, the more are its lobulations.

Arneth* has divided the polymorphonuclear cells into five classes depending upon the number of lobes in the nuclei: horse-shoe, bilobed, trilobed, four lobed and five lobed. He gives as the normal grouping of the neutrophils and eosinophils the following:

Class	I	I	III	IV	V, per cent.
Neutrophils	5	35	41	17	2
Eosinophils	11	69	19	1	2

Arneth claims that the cells in class IV and V, which are the oldest cells, are destroyed first.

The granular leucocytes have as their chief function phagocytosis which depends largely on their ameboid power. This ameboid power is increased as the cells become polymorphous, although ameboid motion is found in all the large mononuclear cells. The power of phagocytosis, however, is limited almost entirely to the polymorphonuclear cells, though myelocytes have been reported to have phagocytic power, and the large endothelial cells which are mononuclear are also actively phagocytic. Bacteria, when they are taken up, are digested very rapidly, due to the presence of a proteolytic ferment.

Opie† has been able to demonstrate not only a proteolytic ferment but also the presence of lipase, amylase, maltase and oxidase enzymes in these cells. The tests for these enzymes are often valuable in differentiating these granular cells in some of the pathological conditions, such as the leukemias, in which at times it is difficult to say whether these cells belong to the series of blasts or to the leukocytic series.

Graham‡ has recommended the following staining methods for differentiating the granular series from the non-granular.

"The method for blood smears.—The smear is allowed to dry thoroughly in the air. Fix one to two minutes in a mixture of nine parts 95 per cent. alcohol and one part of formaldehyde solution (40 per cent. of the gas). The mixture must be freshly prepared.

"1. Wash in water and flood with the following alphanaphthol solution:

Alphanaphthol (Merck's 'Recrystallized' or Merck's 'Reagent')	1.0 gm.
Forty per cent. alcohol	100.0 c.c.
Hydrogen peroxide	0.2 c.c.

Allow a reaction time of four to five minutes.

* Arneth, J., Die neutrophilen weissen Blütkörperchen bei Infections-Krankheiten, Jena (1904).

† Opie, E. L., Jour. Exper. Med., vii (1905), p. 316; viii (1906), p. 410; xi (1907), pp. 391 and 414.

‡ Graham, G. S., Jour. Med. Research, xxxv (1916–17), p. 231.

"2. Wash and place in a dish of running water for about fifteen minutes.

"3. Stain two minutes with the following solution:

Pyronin	0.1 gm.
Anilin	4.0 c.c.
Forty per cent. alcohol	96.0 c.c.

Dissolve the pyronin in the alcohol and add the anilin. The solution keeps well.

"4. Wash in water.

"5. Stain one-half to one minute with a 0.5 per cent. aqueous solution of methylene blue (Grübler's B.X.).

"6. Wash in water; blot. Cover-slip preparations are mounted in balsam. Smears should be made on the slide by touching the slide used as a spreader to the periphery of the drop of blood and allowing the film to follow the spreader as the latter is slowly moved away. This avoids the crushing of the cells often produced by the commonly used technique of forcing the blood drop along in the angle between slide and spreader. Preparations made on the slide may be studied with or without the addition of balsam and a cover-slip. The balsam should be neutral. If acid the granular stain soon fades. An acid balsam may be neutralized by adding to a thin solution dried sodium carbonate that has been heated for several hours in the paraffin oven immediately before use. Shake well, allow to stand for an hour or two, and filter in the oven.

"The resulting picture is much like that afforded by the Romanowsky stains, excepting for the greater prominence of the granules. The neutrophilic granules are usually very abundant, so that the cytoplasmic substance of the cell appears almost completely filled with them. They are somewhat irregular in form and size and are purplish red in color. Occasional cells show fewer and more faintly-stained granules. They may represent old degenerating forms of the cell. The eosinophilic granules are larger, somewhat lighter and more refractile, and have the appearance of spherical bodies with lighter staining centers. The mast cell granule takes a more basic stain so that it appears of a deep purple color. Myelocytes have granules of varying number and size. Erythrocytes are greenish yellow to pink; platelets blue; nuclei of all cells blue; cytoplasm light blue.

"The best results are secured with fresh smears or with such as are not over a few days old. After 10 days to two weeks the reacting substances begin to disappear, so that in older specimens many of the granules fail to stain and some cells may appear entirely devoid of them. The eosinophilic granule retains its staining power much longer than the neutrophilic."

As has been mentioned, phagocytosis is also carried on actively by the large mononuclear or transitional cells. These mononuclear cells have their origin in the endothelial tissue. Mallory* has

* Mallory, F. B., Jour. Exper. Med., v (1900), p. 1.

described these cells as proliferating from the capillary endothelium, but they also arise from the endothelial tissue in the spleen, lymph glands and bone marrow. They can be differentiated by their power to take up vital stains, such as vital red or trypan blue. Just what stimulation causes their appearance in the blood stream is not known. At times they may be found in considerable number. We have seen them markedly phagocytic in diphtheritic exudate along with the ordinary polymorphonuclear phagocytic cells, though often in such cases they are not found in large numbers in the circulation.

During infancy and early childhood the most numerous white cells found are the lymphocytes. They are of two types: The small and the large. The small lymphocytes are about the size of the red blood cells; their nuclei are round and have a strong affinity for basic stains. The chromatin in the nuclei is often irregularly distributed. The protoplasm of the small lymphocytes usually appears as a small rim around the nucleus; it has an especial affinity for basic dyes, though it can be stained less easily with acid or neutral dyes. The large lymphocytes often have a diameter of 20 microns. The nucleus is generally central and round and may be slightly indented. They contain less chromatin than the small lymphocytes. The protoplasm does not stain as deeply with the basic stains as does the protoplasm of the small lymphocytes.

Lymphocytes have slight ameboid movements but do not possess any phagocytic powers. They, however, migrate toward regions of chronic infection rather than in response to active bacterial points of invasion; thus they are found more abundantly around tuberculous infected areas. Murphy* has studied the action of lymphocytes in connection with immunity. He finds that the lymphocyte in some important way controls the tuberculous infection; how this is accomplished is at the present time not known. In acute tuberculous infection, such as miliary tuberculosis, however, the lymphocytes diminish in number; whereas in chronic tuberculous infections they often increase very markedly. A proteolytic ferment has been shown to be present in these lymphocytes by Longcope† and it may be through the action of this proteolytic ferment that the lymphocyte carries on its fight against the tuberculous process. Murphy has pointed out that skin grafts are mainly destroyed by the action of lymphocytes; this also may be due to their proteolytic ferment.

The last formed element normally found in the blood is the platelet. These are small refractile bodies from one to three micromillimeters in diameter. The progenitors of these cells in the bone marrow are the megacaryocytes. The megacaryocyte has a single large

* Murphy, J. B., and Ellis, A. W. M., Jour. Exper. Med., xx (1914), p. 397; Murphy, J. B., and Morton, J. J., Jour. Exper. Med., xxii (1915), p. 204; Murphy, J. B., and Taylor, H. D., Jour. Exper. Med., xxviii (1918), p. 1; Mottram, J. C., and Russ, S., Proc. Roy. Soc. London, Series B, xc (1917–18), p. 1; Murphy, J. B., and Sturm, E., Jour. Exper. Med., xxix (1919), pp. 1, 25, 31, 35; Morton, J. J., Jour. Exper. Med., xxiv (1914), p. 419.

† Longcope, W. T., and Donhauser, J. L., Jour. Exper. Med., x (1908), p. 618.

nucleus, ordinarily ring shaped or basket shaped, composed of a number of smaller nuclei lying more or less fused together. Wright* has shown that these small lobulated nuclei are thrown out by the megacaryocyte and are the platelets of the circulating blood. Megacaryocytes are rarely found in the general circulation, due to their large size. Fragments of megacaryocytes can at times be made out, but they occur only under conditions in which the bone marrow is being very unfavorably affected.

Jordan† has lately confirmed the previous view that these cells arise from the mesameboid elements. Both the megacaryocytes and the platelets are ameboid but they do not possess any phagocytic power.

The main function of the platelets is their action in the coagulation of the blood. They are the source of prothrombin as demonstrated by Bordet‡ and many others.

Platelets vary considerably in size. Normally, the greater number are smaller in size than the erythrocytes; at times, however, large platelets are found in considerable number and these may show granular material often arranged in nuclear form. Under normal conditions platelets number between 200,000 and 400,000 per cm., averaging about 250,000 per cm. Whenever they are diminished in number to 50,000 or 60,000 per cm., the coagulation time of the blood will usually be markedly increased, and spontaneous hemorrhages may be expected, either subcutaneous or in the mucous membranes. This is particularly true of the condition known as purpura hemorrhagica and is a sign of bone marrow aplasia as far as the megacaryocyte element is concerned. In hemophilia, qualitative difference in the prothrombin content of the platelets has been demonstrated by Fonio§ and by Minot and Lee‖.

The platelets may be destroyed in the circulation in certain conditions such as pernicious anemia and in leukemia. They are increased after hemorrhage and during most inflammatory and septic conditions. They are also found increased in chlorosis, which accounts for the complication of thrombosis occurring in this condition. It is to be desired that platelets should be studied routinely in the examination of blood.

Wright and Kinnicutt¶ have described the following method of staining platelets which we have found to be the most satisfactory

* Wright, J. H., Virchow's Arch. f. path. Anat., clxxxvi (1906), p. 55; Jour. Morphol., xxi (1910), p. 263.

† Jordan, H. E., Am. Jour. Anat., xxiv (1918), p. 225.

‡ Bordet, J., Compt. rend. Soc. de Biol., Par., lxxxiii (1920), p. 299; Wright, J. H., Jour. Morphol., xxi (1910), p. 263; Minot, G. R., Arch. Int. Med., xix (1917), p. 1062; Lee, R. I., and Robertson, O. H., Jour. Med. Research, xxxiii (1916), p. 323; Duke, W. W., Jour. Exper. Med., xiv (1911), p. 265; Addis, T., Quart. Jour. Med. Oxford, iv (1910), p. 14; Jour. Path. and Bacteriol., xv (1910–11), p. 427; Howell, W. H., Arch. Int. Med., xiii (1914), p. 76; Minot, G. R., and Lee, R. I., Arch. Int. Med., xviii (1916), p. 474.

§ Fonio, A., Cor. Bl. f. schweiz. Aerzte, xlv (1915), p. 1505.

‖ Minot, G. R., and Lee, R. I., Arch. Int. Med., xviii (1916), p. 474.

¶ Wright, J. H., and Kinnicutt, R., Jour. A. M. A., lvi (May, 1911), p. 1457.

method of counting them, though their number may be roughly estimated in ordinarily well prepared smears stained with Wright's stain. The solutions needed are: (1) An aqueous solution of brilliant cresyl blue, 1 to 300; and (2) an aqueous solution of potassium cyanide, 1 to 1400. The cresyl blue solution is permanent but should be kept on ice. The cyanide solution should be made up of pure potassium cyanide which has not undergone any decomposition and it should be made up at least every 10 days. The two solutions are mixed in the proportion of two parts of cresyl blue to three parts of potassium cyanid solution. They are mixed and filtered immediately before using. The blood is taken up in the ordinary red blood counting pipette in the proportion of 1 to 100. Care must be taken that the mixture of the diluting fluids does not stand for any length of time because there is a precipitate formed. This precipitate does not form, however, after it is mixed with the blood, so that the pipette can be allowed to stand for sometime before the counting is done; but it should be well shaken before making the count. "The platelets appear as sharply outlined, round or oval, or elongated lilac-colored bodies. The red cells are decolorized and appear only as shadows. The nuclei of the white cells are stained a dark blue; the protoplasm, light blue."

The proportions in which the different types of white blood cells exist under normal conditions vary considerably more in infancy than in childhood, and more in childhood than in adult life. In studying the pathological conditions of the blood it is important to know these normal variations. Morse* gives the percentages of the different leukocytes in the blood of infants under two years as follows: Polymorphonuclears, 35 to 45 per cent.; small mononuclears, 40 to 50 per cent.; large mononuclears, 10 per cent.; eosinophils, 1 to 5 per cent.; the total count of white blood cells, 10,000 to 14,000. Rabinowitsch† does not give as high a total count. Between the ages of 1 and 15 years, his counts vary from 6500 to 8000. This certainly does not agree with our findings which agree more nearly with Morse. We do not find that the adult counts are reached until about the tenth year and the adult differentials not until a year or two later. Rabinowitsch's polymorphonuclear neutrophil counts increase from 30 per cent. in the first year to 68 per cent. in the fifteenth year. The small and large lymphocytes diminish from 61 per cent. to 23 per cent. in the same years. Transitional cells vary from 2.5 per cent. to 3.2 per cent.; eosinophils from 3.6 per cent. to 4.1 per cent., with a maximum of 7.5 between the eleventh and twelfth years, and 6.4 during the seventh and eighth years; mast cells from 0.4 per cent. to 0.6 per cent. Before the fifth or sixth year, the lymphocytes exceed the neutrophils, but subsequently the reverse is the case. Karnitsky‡ gives the following table:

* Morse, J. L., Transactions of Am. Med. Ass., Section on Diseases of Children (1908), p. 70.

† Rabinowitsch, D., Arch. f. Kinderh., Stuttg., lix (1912), pp. 161–172.

‡ Karnitsky, A. O., Arch. f. Kinderh., xxxvi (1903), p. 42.

LEUKOCYTE PERCENTAGES IN CHILDREN (KARNITSKY)

Age, years	Total leukocyte count	Percentage of neutrophils	Percentage of lymphocytes	Percentage of eosinophils
1–2	12,500			
2–3	9,400	40.7–30.2	60.0–75.6	
3–4		40.3–32.1	58.0–45.0	
4–5		39.7–34.0	53.0–45.0	
5–6		59.0–35.0	52.0–32.0	Varies
6–8		51.0–37.3	52.0–35.0	greatly
8–10	7,900	62.6–40.0	46.6–24.0	3.8–8.6
10–12		66.6–43.7	39.0–22.0	
12–14		63.5–47.6	40.0–23.0	

Carstanjen's* table is as follows:

LEUKOCYTE PERCENTAGES IN CHILDREN (CARSTANJEN)

Age	Neutrophils, per cent.	Lymphocytes, per cent.	Eosinophils, per cent.	Transitionals, per cent.	Large mononuclears, per cent.
1–6 mo.	34.5	50.0	3.5	10.5	0.5
6–12 mo.	40.8	49.2	0.7	8.2	0.9
1–2 yr.	41.9	47.0	3.0	7.5	0.4
2–3 yr.	48.2	38.4	3.9	8.7	0.7
3–4 yr.	52.6	33.2	5.7	7.9	0.5
4–5 yr.	61.0	25.8	6.3	7.2	0.3

As has already been stated in connection with the red blood cells there are certain physiological variations in the numbers present in the peripheral circulation. It has been pointed out that the red cells are affected by high altitudes; there is an increase in the number of cells and also a tendency for the cells to be somewhat smaller than normal. The first increase on going into a high altitude is due to the fact that the red blood cells held in reserve are called out without in any way affecting or increasing the formation of red blood cells. This is due to the fact that the decreased oxygen supply in high altitudes calls out all the reserve red blood cells to furnish sufficient oxygen for the needs of the body. Later on there is a true increase in blood volume and a real increase in the total number of cells.

In like manner the leukocytes are affected by certain physiological factors which have nothing to do with increased activity either in the bone marrow or other tissues which form white blood cells. As has already been noted, during the first few days of life there is an increase

* Carstanjen, M., Jahrb. f. Kinderh., 3 F. ii (1900,), pp. 215–241, 333–359, 684–720.

in the total blood volume. During this period there may be an increase in the polymorphonuclear cells and the total leukocyte count may run from 15,000 to 30,000. This plethora is apparently purely physiological; at least so far no other explanation has been offered for it. More or less gradually the polymorphonuclear cells decrease, giving the typical blood picture during infancy of an increase in the percentage of lymphocytes over that of polymorphonuclear leukocytes. During digestion, especially during the first hour (sometimes it has gone as long as two, rarely three hours), there is a slight increase in the total number of cells, mainly in the lymphocytes, though there is some increase in the polymorphonuclear cells. This increase is greater the higher the percentage of protein in the food. This may account for the leukocytosis which occurs while the infant is on colostrum, though in this case the increase is greater in the polymorphonuclear leukocytes.

After exercise there is also a moderate polymorphonuclear increase. This is usually comparatively slight unless the exercise is excessive.

METHODS OF COUNTING RED AND WHITE CORPUSCLES

The blood should be taken from the ear, finger or toe. It is essential that the puncture be deep enough so that the blood flows freely without pressure or manipulation as these unquestionably change the relative amount of cells and serum obtained. Some practice is necessary in order to get sufficient amounts of blood and to acquire an accurate technique.

The Thoma-Zeiss counting chamber can be used for estimating both the red cells and the white cells. It is preferable, however, to use either the Zappert or Türk counting chambers as these are ruled so that many more fields can be counted with the same specimen.

Diluting Fluids for Red Cell Count.—For counting red cells, one of the following solutions should be used. Either one of these prevents coagulation and apparently causes no change in the size or shape of the cells if the technique is properly carried out.

Hayem's Solution:

	Gm.
Bichlorid of mercury	0.5
Sulphate of sodium	5.0
Chlorid of sodium	1.0
Distilled water	200.0

Toisson's Solution:

	Gm.
Methyl violet 5B	0.025
Chlorid of sodium	1.0
Sulphate of sodium	8.0
Glycerin	30.0
Distilled water	160.0

For the purpose of counting the white blood cells, a solution must be used which lakes the red blood cells. The usual solution used is a 0.3 to 0.6 per cent. solution of glacial acetic acid. This can be used clear, or a few drops of concentrated aqueous solution of gentian violet may be added to the acid.

Apparatus for Counting Red Blood Cells.—A red blood cell pipette is used. The capillary tube is marked 0.5 and 1.0 and above the bulb it is marked 101 which indicates that the bulb contains 100 times the amount of the capillary tube. The blood is drawn up in the red blood cell pipette to the mark 1.0. The blood should be wiped off the point and then the diluting fluid drawn up to the mark 101 above the bulb. The tube is then rotated rapidly in order to make a complete, uniform mixture. The dilution is now 1 part of blood to 99 parts of diluting fluid. If the blood has been drawn up to the mark 0.5 on the pipette, the dilution would be 1 in 200 instead of 1 in 100.

In delivering the solution to the counting chamber it is important first that all the clear fluid should be blown out of the capillary pipette. It is best to blow out one or two drops of the blood mixture solution and then to put a drop in the center of the counting chamber. It is important that the counting chamber should be clean. The cover-glass is then placed over the chamber. If the drop is of the right size, it will cover the central ruled disk completely without running over into the trough around the central ruled disk. If the drop is too large or too small, accurate results will not be obtained. It takes some slight practice to accomplish this, but without accurate technique at this stage the results will be inaccurate.

The corpuscles are counted with a magnification of about 300. The area of each small square is $\frac{1}{400}$ sq. mm., and the distance between the floor and the lower surface of the cover is $\frac{1}{10}$ mm., so that each square represents $\frac{1}{4000}$ cu. mm. At least 100 small squares should be counted. It is usually satisfactory to start with the upper left-hand corner, going across to the right, then down to the next line of squares and across to the left until 100 squares have been counted. Supposing X to equal the number of cells counted in 100 squares, the calculation then will be,

$$\frac{X \times 400 \times 100}{100} = X \times 4000 = \text{the red blood cells in 1 cu. mm. of blood.}$$

Counting the White Blood Cells.—For this the white blood counting pipette with the larger capillary bore is used, taking the fluid up to mark 1.0. The bulb holds 10 times as much as the capillary tube, therefore the dilution will be 1 to 10; or if there is a leukocytosis, the dilution can be made 1 to 20. In a leukemia it may be advisable to use the red blood cell pipette instead of the white, drawing the fluid up to 1.0 and making the dilution 1 to 100.

The Zappert ruling chamber, as stated, facilitates the procedure in counting a large number of cells. The calculation then would be as follows (X equalling the number of cells counted in 2000 squares),

$$\frac{X \times 4000 \times 10}{2000} = X \times 20$$

Differential Count of White Blood Cells.—To make a proper differential count it is essential that a thin, uniformly spread smear should be made. This can best be done on cover-slip preparations rather than on slides. It takes quite a little experience before a uniformly spread, thin smear can be made, but it is absolutely essential that this be done if an accurate differential count is to be made. Ordinarily too little attention is paid to the smear. If a poorly prepared smear is examined, it will be seen that around the edges the cells are piled up, whereas in the center the distribution is very much more even. However, the fact that the cells are piled up around the edges makes for marked inaccuracy in the differential count.

A minimum of 200 cells should always be counted, but preferably 300 to 500 cells should be counted in order to arrive at reliable results. It is best not only to give percentages but also the absolute count of cells.

Staining Dried Films.—The best staining fluids are some modifications of the Romanowsky stain such as the Wright stain which is most generally used in this country. The film is dried in the air, then covered with staining fluid, about 10 or 12 drops being sufficient for a cover-slip preparation. After 30 seconds, twice the amount of distilled water is added to the stain and this is allowed to stay on for from three to five minutes, depending on the blood preparation, and then is washed off with water and the cover-slip dried. If the smear is overstained, it will show a very deep red or greenish tint. This can be remedied by allowing a few drops of distilled water to remain on the slide for several minutes, after which it may be washed off and dried.

The stained specimen can be mounted in balsam and then studied with the oil immersion lens. It is necessary that the balsam should not be acid, for an acid balsam decolorizes the specimen. If cedar oil is used on unmounted specimens, it can be removed after counting without spoiling the stain by washing off with xylol.

In estimating blood counts, reference may be made to some atlas of hematology such as "Atlas of Hematology," by Karl Schleip; "The Bone-Marrow," by W. E. Carnegie Dickson; "Clinical Diagnosis," by C. P. Emerson; or "Clinical Diagnosis," by C. E. Simon.

The following blood examination report is the one we have been in the habit of using.

BLOOD EXAMINATION REPORT

Name: *Location:* *Date:*

Hemoglobin: Method:
Red Count: Color Index:
White Count:
Differential, Cells Counted:
Neutrophils:
Small Lymphocytes:
Large Lymphocytes:
Endothelials:
Basophils:
Eosinophils:
Fragmented Leucocytes: Type:
Vacuolated Leucocytes: Type:
Unclassified:

Smear, (1) Red Cells,
Staining,
Achromia: Degree:
Polychromatophilia: Degree:
Stippling: Frequency:
Nuclear Degenerations: Frequency:
Inclusion Bodies: Frequency:
Size,
Anisocytosis: Degree:
Microcytes: Number:
Macrocytes: Number:
Megalocytes: Number:
Shape,
Poikilocytosis: Degree:
Abnormal Forms:
Normoblasts: Number:
Erythroblasts: Number:
Megaloblasts: Number:
Poikiloblasts: Number:
Microblasts: Number:
Macroblasts: Number:
(2) Platelets,
Number:
Size:
(3) Abnormal White Cells,
(*a*) Lymphocytic series
Prelymphocytes: Number:
Türk forms: Number:
(*b*) Myeloid series
Myelocytes
neutrophilic: Number:
basophilic: Number:
eosinophilic: Number:
Premyelocytes: Number:
Myeloblasts: Number:
(*c*) Endothelial phagocytes
(4) Parasites, especially malarial,

REMARKS:

Signed:

There may be some criticism because of using the differential nomenclature which is here employed, especially in connection with

endothelial cells; but as long as this point has not been definitely settled we have been in the habit of using the above differential nomenclature.

Routine estimation of the number of cells in circulation and the estimation of the percentage of hemoglobin yield valuable but incomplete data which concern only the concentration of the blood and do not furnish absolute values for red cells, for hemoglobin, nor for the oxygen carrying capacity of the blood. These enumerations and estimations of the hemoglobin may make an anemia seem more apparent than real. It might depend on a marked increase in the blood volume, while a polycythemia may not necessarily mean an absolute increase in the red cells or in the hemoglobin but may depend on the decrease in the blood volume. In order to obtain absolute values for either red cells or hemoglobin, plasma volume or total blood volume estimates must be made.

The volume as well as the concentration of the blood plays an important rôle in the pathological physiology of the blood. The normal values for plasma and blood volume are best expressed in percentages or fractions of the body-weight or as number of cubic millimeters per kilogram of body-weight.

Welcker* found that blood constituted one-thirteenth of the body-weight. He obtained this by bleeding animals to death; he washed out their blood-vessels with water, then minced and washed the tissues thoroughly, brought the blood and washings together, and determined their hemoglobin content.

Haldane and Smith† modified the method of Gréhant and Quinquaud.‡ In this method a measured amount of carbon monoxide was inhaled and its percentage content determined in a small sample of blood. They made the patients breathe for five minutes a measured quantity of carbon monoxide and then estimated the carbon monoxide content by the carmin titration method of Haldane. They found by this method that the blood volume was one-twenty-first of the body-weight.

Plesch and Oerum§ employed this same method but determined the carbon monoxide volumetrically and found the blood volume to be one-nineteenth of the body-weight.

Behring‖ estimated the blood volume by injecting tetanus antitoxin which he had observed remained in the circulation for long periods. By this method he estimated the blood to consitute $\frac{1}{11.8}$ of the body-weight. With this same method Kämmerer and Waldmann¶ in

* Welcker, H., Bestimmungen der Menge des Körperblutes und der Blutfärbekraft, sowie Bestimmungen von Zahl, Maass, Oberfläche und Volumen des einzelnen Blutkörperchens beim Thier und beim Menchen, Präger Vrtljschr., iv (1854), p. 11; Ztschr. f. rat. Med., iv (1858), p. 145.

† Haldane, J., and Smith, J. L., Jour. Physiol., xxv (1899–1900), p. 331.

‡ Gréhant and Quinquaud, Compt. Rend. Acad. Sc., xciv (1882), p. 1450.

§ Oerum, H. P. T., Deutsch. Arch. f. klin. Med., xciii (1908), p. 356.

‖ Von Behring, E., München. med. Wchnschr., lviii (1911), p. 655.

¶ Kämmerer, H., and Waldmann, A., Deutsch. Arch. f. klin. Med., cix (1913), p. 524.

Müller's clinic obtained a value of $\frac{1}{10.2}$; while Fries* obtained a value of $\frac{1}{12.6}$.

Keith, Rowntree and Geraghty† first used the vital dye method (vital red) for estimating the blood volume. By this method they found that the normal blood volume for adults is about 8.8 per cent. or $\frac{1}{11.4}$ of the body-weight.

Whipple‡ and his associates have used brilliant vital red in estimating the blood volume in dogs and have found the average blood volume to be 10.1 per cent. of body-weight. Lucas and Dearing§ have used this method during early infancy. In newborn infants the blood volume varied from 10.7 per cent. to 19.5 per cent. of body-weight and from 107 c.c. to 195 c.c. per kilogram of body-weight. The pigment volume which, as Whipple has pointed out, is an exceedingly valuable index of the curve of blood regeneration and is obtained by multiplying the hemoglobin per cent. by the blood volume, varied from 304 c.c. to 899 c.c. In infants over 15 days the blood volume was found considerably more constant, varying from 9 per cent. to 12.6 per cent., with an average of 10.9 per cent.

The vital dye method for estimating blood volume is the most satisfactory at the present time. The dye is non-toxic when injected intravenously, even in large doses, 15 times that used in the estimation of plasma volume. The dye is not taken up by any of the red blood cells or tissues but remains for a comparatively long time in the plasma and it can be easily and accurately determined by colorimetric methods. During infancy the longitudinal sinus makes it very easy to carry out this procedure, especially if Goldbloom's‖ block is used. In older children the jugular veins or the veins at the elbow can be used. The procedure is as follows:

Ten cubic centimeters of blood are withdrawn into a record syringe which has been sterilized and thoroughly washed out with sterile salt solution. This first sample of blood is immediately discharged into an accurately calibrated 15 c.c. centrifuge tube (hematocrit tube) which contains 2 c.c. of 1.6 per cent. solution of sodium oxalate. The blood and oxalate are thoroughly mixed by inverting the tube several times so as to obviate any possible clotting. The centrifuge tube is then stoppered. From this tube the hematocrit readings are made and the serum for making the standard control dye mixture is taken. Before this first sample of blood is taken the standard amount of dye solution is drawn up into a record syringe along with enough normal (0.9 per cent.) saline solution to make sure that all the dye has been taken up into the syringe from the small containing dish in which the measured amount of dye is placed. The dye solution is a 1.5 per cent. solution and is given

* Fries, H., Geburt und Wochenbett, Ztschr. f. Geb. u. Gyn., lxix (1911), p. 340.

† Keith, N. M., Rowntree, L. G., and Geraghty, J. T., Arch. Int. Med., xvi (1915), p. 547.

‡ Whipple, G. H., Amer. Jour. Physiol., li (Mar., 1920), pp. 205–278.

§ Lucas, W. P., and Dearing, B. F., Amer. Jour. Dis. Child., xxi (1921) p. 96.

‖ Goldbloom, A., Am. Jour. Dis. Child., xvi (1918), p. 388.

in the amount of 1 c.c. per 5 kg. of body-weight, which gives 3 mg. of the dye per kilogram. The dye solution is injected into the sinus immediately after the first 10 c.c. of blood have been withdrawn, using the same needle only changing the syringe, the dye being completely washed out by drawing blood back and forth several times into the syringe after the dye has been emptied out of the syringe into the sinus. The needle is then withdrawn; exactly four minutes after the injection of this dye a clean needle is again inserted into the sinus and a sample of 16 c.c. of blood is withdrawn and discharged immediately into two vaselined test tubes about equally distributed. This furnishes the plasma for the estimation of the blood plasma volume. All the tubes are now placed in the ice chest for at least half an hour, then centrifuged at 2500 revolutions a minute for half an hour. In the hematocrit tube (accurately calibrated centrifuge tube) the total amount of fluid is noted and the number of cubic centimeters of blood cells, red and white, are noted. This gives the total hematocrit reading when 2 c.c. are subtracted for the oxalate dilution and the hematocrit reading for the red blood cells. Five cubic centimeters of this serum are pipetted off and to this is added 5 c.c. of a 0.9 per cent. sodium chloride solution (normal saline) and 5 c.c. aqueous dye solution. This dye solution is made up as follows: 0.5 c.c. of a 1.5 per cent. brilliant vital red is pipetted into a 100 c.c. volumetric flask which is then filled up to the mark with distilled water. This gives the standard against which is read the unknown dye-colored plasma. The dye-colored serum is pipetted off from the vaselined tube and 2 c.c. of this serum is diluted with 4 c.c. of 0.9 per cent. sodium chloride solution, which gives the same dilution to this serum as the standard dye solution made from patient's dye-free plasma, to which has been added a known amount of dye and salt solution. After mixing thoroughly, the standard dye plasma solution and serum solution are allowed to stand for 15 minutes so that the intensity of color may be uniform. The standard dye solution is then put into the colorimetric wedge (we have used in all our work the Hellige colorimeter and have found it perfectly satisfactory; it has been tested against the Dubosc and found accurate) and each of the samples of the unknown serum dye solution is read against this. The average of three readings is taken as the color percentage of the sample.

Computation Results.—From the hematocrit readings the plasma per cent, and the red cell per cent. may be easily calculated—the red cell per cent. is read from the hematocrit tube reading by the total hematocrit reading minus 2 and the plasma hematocrit reading by subtracting the total cell hematocrit reading fron the total hematocrit reading minus 2.

$$\text{Plasma volume in c.c.} = \frac{\text{Weight in kilograms} \times 40}{\text{Average colorimetric reading}} \times 100$$

$$\text{Blood volume in c.c.} = \frac{\text{Plasma volume}}{\text{Plasma per cent.}} \times 100.$$

The plasma per cent. means the percentage of whole blood which the plasma constitutes and is obtained by dividing the total number of cubic centimeters of oxalated plasma present in the hematocrit tube minus 2 by the total contents of the tube in cubic centimeters minus 2. The red cell per cent. is calculated from the hematocrit tube by dividing the red cell reading by the total hematocrit reading minus 2. The blood volume is divided by the body-weight in kilograms which gives the blood volume in cubic centimeters per kilogram of body-weight, and the percentage of blood to body-weight is derived from this figure by simply pointing off one place. The pigment volume is obtained by multiplying the hemoglobin per cent. by the blood volume.

In pathological conditions, the changes from the normal blood volume are quite striking. For example, the blood volume following severe diarrheas is markedly decreased; in these cases the hematocrit readings show a very marked relative increase in the red blood cells and a diminution in the plasma volume. In the chronic intestinal nutritional conditions, such as athrepsia, the blood volume is also diminished; but the plasma volume in these cases is relatively increased at least, whereas the red blood cell volume is actually decreased. In anemias, even where the total blood volume is not markedly lowered, there is a change in the relative percentage of plasma and cells, for there is a relative increase in the plasma and a diminution in the red blood cell percentage. In both chronic nutritional conditions and anemias the plasma volume may be as high as 80 per cent. of the total hematocrit reading. Marriott* has reported the same findings as Lucas and Dearing† have reported of diminished blood volume in acute diarrheas and cases of athrepsia.

Tables I and II show the variations in blood volume as done by various authors using various methods, and also some of the blood volumes as determined in normal and pathological conditions.

Robertson and Bock‡ have used the dye method in estimating the blood volume following traumatic loss of blood. Their conclusions are discussed elsewhere in another connection.

* Marriott, W. Mck., Amer. Jour. Dis. Children, xx (1920), p. 461.

† Lucas, W. P., and Dearing, B. F., Amer. Jour. Dis. Children, xxi (1912), p. 96.

‡ Robertson, O. H., and Bock, A. V., Jour. Exper. Med., xxix (1919), Article No. I, p. 139; Article No. II, p. 155.

TABLE I.—VARIATIONS IN BLOOD VOLUME BY VARIOUS AUTHORS USING VARIOUS METHODS

	Bischoff, Welcker, direct method	Amount blood pumped in one second, Vierordt, indirect method	Estimated solids before and after water injection, Lehman, indirect method	Gréhant and Quinquaud, carbon monoxide, Haldane and Smith	v. Behring, antitoxin	Kämmerer and Waldmann, antitoxin	Fries, antitoxin	Keith, Rowntree and Geraghty, dye
Blood volume	1/13	1/13	1/8	1/21 1/19	1/11.8	1/10.2	1/12.6	8.8%
Plasma volume	...	...	...	... ...	....	....	....	1/11.2
								42 to 56 c.c.
								5%
								1/23 to 1/17 of body weight
Blood per kilogram of body-weight	...	...	...	... ...	....	....	....	85 c.c.
Plasma per kilogram of body-weight	...	...	...	... ...	....	....	....	56.9% of total blood
								50 c.c.
				(Plesch)				
Blood per cent. of body-weight	1/13	1/13	1/8	1/21 1/19	1/11.8	1/10.2	1/12.6	8.8%
								1/11.4
								(1/13 to 1/10.5)
Per cent. of erythrocytes	...	...	...	... ...	....	....	....	43%
Per cent. of plasma	...	...	...	... ...	....	....	....	57%

TABLE II.—VARIATIONS IN BLOOD VOLUME IN DIFFERENT PATHOLOGICAL CONDITIONS AND IN NORMAL INFANTS (DYE METHOD)

	Keith, Rowntree and Geraghty					Lucas and Dearing			Marriott	
	Pregnancy	6 cases obesity	10 cases emaciation and anemia	3 cases pernicious anemia	2 cases polycythemia	Normal 50 newborn	Normal to one year	3 cases secondary anemia	7 cases normal under one year	11 cases athreptic
Blood volume	Before labor, 9.56% After labor, 9%	3%	1/13.2	Normal 1/11	.....	10.7% to (14.7) 19.5%	9 % to 12.6 Av. 10.9%	7.4 to 11.8 %		
Plasma volume	After labor, 4.9%	3.8%	56 c.c.	72 c.c.						
Blood per kilogram of body-weight	.....	51 c.c.	78 c.c.	.....	73 c.c. to 113 c.c.	107 c.c. to (147) 195 c.c.	90.3 to 114 c.c.	74.5 c.c. to 118 c.c.		
Plasma per kilogram of body-weight	Before labor, 58.4 c.c.	37.1 c.c.	56 c.c.	72 c.c.	39 c.c. 60 c.c.					
Blood per cent. of body-weight	.....	.....	.....	.....	.....	.....	.....	.....	9.1 % 8.0 to 10.8	8% 4.8 to 10.4
	Obstetrical reports showed a loss of 300 c.c.									
	Blood volume studies 1100 c.c.									

Lately, Bock* has shown the constancy of plasma volume in various conditions. The summary of his findings is given in the following table:

AVERAGE RESULTS

No. of cases	Diagnosis	Weight in kg.	Plasma in c.c. per kg.	Blood in c.c. per kg.	Total plasma, fraction of body-weight	Total plasma, per cent. of body-weight	Total blood, fraction of body-weight	Total blood, per cent. of body-weight
5	Normal	67.0	51.0	81.0	1/19.6	5.1	1/12.2	8.2
3	Polycythemia	54.5	51.6	128.0	1/19.3	5.1	1/7.8	13.7
7	Pernicious anemia	52.3	49.3	58.5	1/20.4	4.9	1/17.3	5.7
7	Miscellaneous	58.4	49.4	70.7	1/20.3	4.9	1/14.0	7.1
8	Diabetes	50.4	48.0	75.5	1/20.8	4.8	1/13.5	7.3

Note.—Table taken from "The Constancy of the Volume of the Blood Plasma," by A. V. Bock, M.D., Arch. Int. Med., xxvii (Jan. 1921), No. 1, p. 83. —taken from Table 7, p. 91.

We have already referred to the alterations which occur in the formation of red blood cells and the oxygen capacity of the blood as affected by elevation and barometric pressure. These changes, as has been pointed out, are due primarily to changes in the response of the bone marrow to increased activity which in turn is due to the lessened oxygen capacity of each individual cell, and there is an increase in the total blood volume at high elevations. Normally there is undoubtedly quite a reserve both of red cells and of leukocytes which can be called out very rapidly; at the same time, whatever factor calls out this excess supply stimulates the bone marrow to further increased production.

Whipple has shown that, following acute and chronic hemorrhages, a very marked increase in the production of red blood cells takes place. When the hemorrhage amounts to approximately 50 per cent. of the total blood volume, the regeneration will be very rapid. If, however, there are repeated hemorrhages which keep the level at this point for a considerable period or if the dietetic factors are so regulated that there is a high carbohydrate food given and no blood forming foods, the recovery will be very much more gradual; in fact, if these conditions are continued for any length of time, it may be impossible to bring the blood up to its normal original level. In other words, a slight secondary anemia will be more or less persistent.

However, following such hemorrhages there is no destruction; the process is one of pure regeneration. The red cells will always regenerate more rapidly than the percentage of hemoglobin. The reticulated cells showing active regeneration will be at first definitely increased; at times following hemorrhage they may reach as high as 10 per cent. However, this will gradually fall as the red cells and hemoglobin

* Bock, A. V., Arch. Int. Med., xxvii (1921), p. 83.

return to their normal; so that within two weeks following an acute hemorrhage the percentage of reticulated cells is usually under 2 per cent., which may be taken as the upper limit of the normal. Their appearance is a good indication that regeneration is advancing satisfactorily.

At times, following severe hemorrhage, nucleated red cells will be found in the blood. These are to be taken to indicate that the hemorrhage has called out not only the reserve red blood cells but the immature and earlier forms of red blood cells. They do not indicate a pathological condition but rather that the bone marrow is acting normally to the stimulation caused by the hemorrhage.

Following this, there will also be an increase in the polychromatophilic cells and platelets. These may be increased at times as high as 1,000,000 per cubic millimeter. The granular leukocytes are increased and at times myelocytes may be quite numerous in the blood stream.

The lymphocytes are not increased following hemorrhage, thus showing that the stimulation of hemorrhage is mainly on the bone marrow portion of the blood forming organs and does not call on the lymphatic system. In chronic hemorrhage, as has been stated, the stimulation gradually diminishes and more typical forms of red blood cells both as to size and shape may be found. In such cases there is less of an increase in the reticular cells than in the normoblasts and what blasts appear are often the small forms, the microblasts.

We are well acquainted with the increase in the leukocytes to infection or the injection of foreign proteins. This is evident in almost all acute infections. At first the surplus leukocytes migrate to the area of infection. An excess of leukocytes is found in the circulation. The bone marrow is stimulated to an increased production of leukocytes which will continue for a variable time, usually as long as the infection is present unless there is an overwhelming toxemia which causes a lessened production or a diminished rate of production so that the leukocyte count falls to nearly normal, or in extreme cases there may be a leukopenia. When dead bacteria, such as typhoid bacilli, are given intravenously, the first response is a short period in which the leukocytes are diminished. This period of leukopenia is often a very short one and is followed by a long-continued leukocytosis. The primary leukopenia may be due to the fact that the leukocytes are immediately attracted to the point of infection and that the leukocytosis represents the later call on the surplus leukocytes and the continued increased production by the bone marrow. In ordinary typhoid fever, however, there is a leukopenia. The same is true of the ordinary infection by the tubercle bacillus. Just why there is this marked difference between the ordinary response of the leukocytes by a leukopenia in clinical typhoid fever and on the other hand a marked leukocytosis to an intravenous injection of dead bacilli is not known.

Following hemorrhage, as has been stated, there is a marked increase in the polymorphonuclear leukocytes. This begins almost immediately, reaches its height in about two or three hours, and may

remain at a high level for several days. In this case, as in leukocytosis following trauma, the cause is probably the introduction into the blood stream of foreign protein material, such as tissue juices.

There are certain infections which call out an increase in the eosinophilic granular leukocytes. In eczema (the exudative diatheses), bronchial asthma, intestinal parasites and myelogenous leukemia we get varying increases in the eosinophils. During all these infections there is a definite hyperplasia of the bone marrow, especially of the islands that produce the granular leukocytes. Parallel with this in some of the infections, such as that caused by streptococcus, there may be a definite destruction of the red cells, probably in the circulation, which accounts for the usual picture of leukocytosis with diminution in the red cells and hemoglobin found in most acute infections.

Lymphocytosis, as already noted, is normally present in the blood of the newborn. A moderate lymphocytosis is also present in most of the nutritional conditions of infancy. This lymphocytosis is ordinarily associated with an increase in the glandular system, and the enlarged lymph nodes so frequently met with in these conditions show clearly that hyperplasia is going on. During infancy and childhood certain infections are very characteristically associated with a lymphocytosis, measles and whooping-cough particularly so. In the other contagious diseases, such as scarlet fever and diphtheria, there is less tendency to lymphocytosis, though this may be quite evident if the total number of cells is counted rather than relying on simply a percentage increase. In non-infectious diarrheas and in low-grade bronchopneumonias, at times an absolute increase in the lymphocytes as well as in the polymorphonuclear cells will be found.

Murphy and his associates* have shown that the lymphocytes respond very definitely to infections by the tubercle bacillus. There is a hyperplasia of the lymphoid tissue. In administering heliotherapy, in *x*-ray treatment and in radium treatment, there is also at times an increase in the lymphocytes.

BLOOD DESTRUCTION

The life of the red blood cell has been estimated by Ashby† to be 30 days or more. This she has done by transfusion of blood, but where the red cells are destroyed or how they are destroyed is not known. The fact that the bone marrow constantly furnishes new red blood cells and the fact that there is continually an excretion of bile pigment which amounts to about one-fifteenth of the total red blood cells point to a constant destruction.

Wilbur and Addis‡ in discussing the various theories as to the origin of urobilin (urobilin in this connection is applied to the derivatives of blood and bile pigments containing the pyrrol nucleus), "assume that as a rule the presence of urobilinuria is indicative of the

* Jour. Exper. Med., xx, xxix (Oct., 1914), pp. 397, 1919.
† Ashby, W., Jour. Exper. Med., xxix (1919), p. 267.
‡ Wilbur, R. L., and Addis, T., Arch. Int. Med., xiii (1914), p. 235.

fact that bile is reaching the intestine, and that large amounts of urobilin in the urine usually mean that there has been either abnormal destruction of red blood corpuscles, or an insufficiency of the liver to perform its normal functions. A large amount of urobilin in the stool indicates increased blood destruction. Urobilinuria frequently disappears in severe diarrhea. Although urobilin is normally present in the urine in small quantities, its presence cannot be ascertained by the ordinary qualitative tests—a positive reaction with Schlesinger's zinc acetate test or Ehrlich's aldehyde test is not found in normal urine. It is increased in many pathological conditions. It is commonly increased in infectious diseases, in diseases in which there is widespread hemorrhage, traumatic or otherwise, in pernicious anemia, malaria, cardiac decompensation, various forms of liver and gall-passage disease, and in numerous intoxications such as those due to alcohol, chloroform, lead and carbon monoxide."

Thus they accept the enterogenous theory (Friedrich von Müller) of the formation of urobilin in preference to the hematogenous, hepatogenous, nephrogenous or histogenic theories.

Urobilin in Urine and Stools.—The method for estimating urobilin in the urine and stools as adopted by Wilbur and Addis* is as follows:

Urine.—"The method of collection of the 24-hour urine has a considerable effect on the total spectroscopic reading. The vessel in which the urine is collected should be of dark brown glass and should be kept in darkness. Thymol crystals should be added, for even in cases in which no obvious fermentation had occurred we sometimes found a diminution in the total amount if no preservative was present. After measuring the amount of the 24-hour urine, 10 c.c. are mixed with 10 c.c. of a saturated alcoholic solution of zinc acetate, and after a few minutes filtered. If a number of urines are being examined at the same time it is convenient to have test-tubes graduated to 10 and 20 c.c. Ten cubic centimeters of the filtrate are taken and 1 c.c. of Ehrlich's solution is added. It was found that this amount produced a sufficient concentration of acid in the mixture to give the maximum intensity of the urobilin band and contained enough of the paradimethylamidobenzaldehyd for the reaction with urobilinogen. The development of the urobilinogen band is not instantaneous. We found that as a rule it had attained its full intensity in a quarter of an hour. The action can be greatly accelerated by heating, but this is to be avoided. It is better to wait for an hour before making the reading, and during this time the solution should be kept in the dark. After three or four hours there is a diminution of the urobilin and urobilinogen in filtrates from urines, so the estimation should be made not later than three hours after adding the Ehrlich solution. We found that Citron's hand spectroscope was the most convenient instrument to use. The filtrate was washed into a graduate and diluted

* Wilbur, R. L., and Addis, T., Arch. Int. Med., xiii (1914), p. 235—method quoted from pp. 247–248.

with tap-water until one and then the other bands of light absorption had disappeared when the full amount of light entered the spectroscope, but were still visible when the light was partly shut off. This gives a fairly definite end-point, and we did not find any great variation in the readings made by different persons. It is important of course that the light shall be always of approximately equal intensity. We made the readings in a dark room with a Tungsten electric bulb, holding the spectroscope close to the source of light. In highly colored urines one may be in doubt as to whether or not a trace of urobilin is present, for there may be so much general absorption of light as to obscure the urobilin band in the undiluted filtrate. There is no such difficulty with the urobilinogen band which lies between the red and yellow where there is no marked light absorption. With urines containing bile, if the amount of urobilin is not very large, it is necessary to add some fullers' earth and to leave the mixture standing for some time before filtration. If this is done the urobilin band can usually be read even in the undiluted filtrate. The dilution required gives the value for 5 c.c. of urine. If this figure is multiplied by the number of 5 c.c. quantities in the 24-hour urine, the number of dilutions which would have been necessary if all the urobilinogen and urobilin in the 24-hour amount had been concentrated in a volume of 5 c.c. is obtained. For instance, if in a 24-hour urine measuring 1000 c.c. a reading of 10 dilutions for urobilinogen and of 20 for urobilin were made, the total urobilin would be $30 \times 200 = 6000$. We tried to determine the dilution value of definite weights of urobilin prepared from bilirubin, but different preparations varied so much in their dilution value that it was obvious that we were not dealing with pure urobilin and we abandoned any attempt to express our results in milligrams of urobilin.

Stools.—"All the feces passed in the 24 hours were collected in the same receiver, the stools being protected from light. They were then washed into a large graduate and thoroughly ground up with water into a homogeneous paste, and water added to 0.5, 1, or if necessary 2 liters, depending on the quantity of stool. After thorough mixing, 25 c.c. were taken and 75 c.c. of acid alcohol (95 per cent. alcohol, 1600 c.c.; concentrated hydrochloric acid, 25 c.c., and water, 800 c.c.) were added. The mixture was then put into a shaker for about half an hour. A considerable number of extractives were tried for removing the urobilin from the stools, but none were found so efficient as alcohol with hydrochloric acid. After thorough mixing in the shaker an equal quantity of a saturated solution of zinc acetate in alcohol was added and the mixture was filtered. After adding 2 c.c. of Ehrlich's reagent to 20 c.c. of the filtrate, the solution was put aside in a dark place until next day. The addition of zinc acetate is not absolutely essential, but in some cases we observed an intensification of the urobilin band following its use, and it is perhaps an advantage to make the urine and stool readings as far as possible under the same conditions. The development of the urobilinogen band was not always

complete until six hours had elapsed, but thereafter there was no loss of urobilinogen or urobilin for a long time, although this was not the case with the zinc acetate filtrates before the addition of Ehrlich's solution. The reading was made in the same way as with the urine and the total amount calculated for the volume of stool after grinding up with water, the dilution of the 25 c.c. by acid alcohol and zinc acetate being taken into account. Instead of using tap-water for dilution of the final extract, 60 per cent. alcohol was required to avoid the development of a precipitate."

Rous and Robertson* have shown that red blood cell destruction does not take place by phagocytosis nor ordinarily by hemolysis. They have shown, however, that destruction does take place by fragmentation. Fragments of red blood cells are found in the spleen. In the circulation, evidences of destruction are shown by the presence of poikilocytosis and of small red blood cells, microcytes. Abnormal shape of the red blood cells is usually taken as an evidence of beginning destruction; this goes on to fragmentation, and finally the red blood cell becomes nothing but dust. This is removed by the spleen and broken up by the liver; though, as Whipple and his associates† have shown, pigment formation may take place in the serous cavities, and where the liver is entirely cut off, other tissues will take over the function of pigment formation.

The evidence that the spleen plays a large role in red blood cell destruction is shown by the fact that there is a high iron content in the spleen and also that in the spleen there is found intracellular and extracellular blood pigment. However, it has been impossible to show experimentally that there is an excess of hemoglobin pigment in blood leaving the spleen compared with that entering the spleen; nor has it been proved that splenic extracts increase hemolysis, though suggestive evidence has been offered on this point. The liberation of hemoglobin from the red cells must take place very gradually, for we know that if hemoglobin is liberated rapidly, definite symptoms, such as temperature, will appear and hemoglobin will be recovered in the urine. That other organs besides the liver and the spleen take part in this or at least in the transformation of hemoglobin into bile pigment has been pointed out by Whipple.

Sellards and Minot‡ have shown that hemoglobin properly prepared can be injected intravenously without any toxic symptoms. They have also shown that, where hemolysis has been produced, red blood cell stroma appears when hemolyzed blood is centrifuged. This red blood cell stroma, they think, accounts for the temperature and other toxic reactions which occur when hemolysis takes place intravascularly.

* Rous, P., and Robertson, O. H., Jour. Exper. Med., xxv (1917), pp. 651 and 665.

† Whipple, G. H., and Hooper, C. W., Jour. Exper. Med., xxiii, No. 1 (Jan., 1916), pp. 137–147.

‡ Sellards, A. W., and Minot, G. R., Jour. Med. Research, xxix (1916), p. 469; xxxii (1917), p. 161.

Drinker and Brittingham* have shown that sodium citrate will produce a certain amount of hemolysis and they suggest that this is perhaps the cause of certain unfavorable reactions that occur when citrated blood is used for transfusion. It is probably true that certain toxins produce hemolysis, but whether these hemolytic substances obtained from certain bacteria are true lysins has not been determined.

In diseases such as congenital hemolytic jaundice it is easy to demonstrate that the red blood cells are more easily hemolyzed by hypotonic solutions than normal red blood cells. Increased fragility, therefore, is one of the conditions which lends itself to increased blood destruction. In paroxysmal hemoglobinuria there is apparently no change in the fragility of the corpuscles; but there is present a hemolysin in the patient's serum which acts much in the same way as when transfusion is made from a donor who does not belong to the same group as that of the patient or where the donor's serum is hemolytic to that of the patient's red blood cells. (This particular phase will be discussed in connection with the problem of transfusion.)

The problem of the destruction of erythrocytes and the final disposition of hemoglobin is intimately associated with the whole problem of pigment metabolism. Whipple and Hooper† have shown in their experimental work on bile pigment metabolism that a carbohydrate diet will raise the bile pigment from 50 to 100 per cent. Their experiments with blood feeding showed that this had no influence on the secretion of bile pigment in the normal dog and that, although this diet is rich in pyrrol nucleus, it had no effect on bile secretion. They concluded that hemoglobin is not one of the building stones from which the body constructs its various pigments. Neither did they find that splenectomy, under normal conditions, had any influence on the output of bile pigments. Bile feeding increases very definitely the bile flow in an Eck fistula dog, but it causes at the same time a diminution in the outflow of bile pigments in spite of its active cholagogue action. If the liver had simply an eliminative function in the disposing of worn out corpuscles and hemoglobin by way of the bile, one would expect an excess of bile pigments to be swept out by the cholagogue action of the bile.

Whipple's experiments on bile circulation do not give any evidence that bile pigment absorption occurs from the intestine and they feel safe in claiming that there is no bile circulation of the bile pigment as such.

Addis‡ gives what would appear to be a very simple and direct type of pigment circulation. He suggests that the following outline may cover much of the life history of hemoglobin pigment: "Hemoglobin is constantly liberated in the body from the disintegration of

* Drinker, C. K., and Brittingham. H. H., Arch, Int. Med., xxiii (1919), p. 133.

† Whipple, G. H., and Hooper, C. W., Amer. Jour. Physiol., xlii, No. 2 (Jan., 1917).

‡ Addis, T., Arch. Int. Med., xv (1915), p. 413.

worn out red cells. This hemoglobin is changed in the liver to bile pigments and excreted into the intestine. The bile pigment is reduced to urobilinogen in the intestine, a part escaping in the feces, and an important part being absorbed into the blood, polymerized into urobilin-complex, and taken up by the liver. This portion is stored in the liver or synthesized into hemoglobin, or, if the liver is abnormal, may escape into the blood and appear in the urine as urobilinogen. This hypothesis in a word is 'bile circulation' again presented in a more elaborate form—a circulation of a pyrrol complex."

Whipple felt that this explanation may be admitted as true but claims that there is no evidence that urobilinogen is absorbed from the intestine into the blood as urobilinogen in the portal circulation. It may be admitted that the pigment radicle of hemoglobin may appear in the bile as bile pigment and later as stercobilin or urobilinogen in the intestine.

Urobilinogen, like other pigments, may be produced at times in the liver, but there is no evidence so far that will fit this hypothesis as well as or better than the usual theory that urobilin is formed only in the intestine. In support of this theory, Whipple points out that dogs kept under observation for months and years with bile excluded from the intestine fail to develop any anemia, which shows that the dog is in no way dependent for its supply of hemoglobin upon pigment absorbed from the intestine. This does not preclude the possibility of pigment being absorbed from the intestine, but at least this absorption is of trivial importance in the pigment metabolism. Urobilin, like bile pigments, may at times be formed in one organ or another from some related pigment substance.

It is interesting to note that although bile fed by mouth has an active cholagogue action, it also produces an inhibition of bile pigment output. This decrease may be as great as 50 per cent. of the normal in spite of the cholagogue action. Whipple felt that this strengthens the argument that bile pigment is formed in some other manner than through disintegration of red cells and hemoglobin.

Whipple and his associates say: "As we find more substances (organic or inorganic) which influence promptly the secretion of bile pigments, may we not suspect that these pigments are manufactured in considerable degree by some organ which reacts promptly to various stimuli? It required the widest stretch of the imagination to picture these various simple substances as influencing the red cell katabolism—one group causing prompt and extensive red cell destruction, and the other group equally prompt inhibition. Is it not very probable that these substances react on an organ busy in the production of pigments, and cause it to produce more or less pigment of a certain type?"

As Hooper* has pointed out, various biles act differently. Taurocholic acid has more of a cholagogue action than glycocholic acid but has very little if any action on bile pigment secretion. Glycocholic

* Hooper, C. W., Amer. Jour. Physiol., xliii, No. 2 (Jan., 1917).

acid causes, if anything, a pronounced inhibition of bile pigment output. Bile fat (simple ether extract) is also capable of depressing the curve of bile pigment secretion, while it does not influence the output of bile.

Cholesterol is an inert substance as regards any control of bile pigment secretion. Cholic acid has little effect on bile flow but may decrease somewhat the bile pigment output.

These variations probably explain the variations in the action of bile from different animals, as these substances vary considerably in different animals.

Whipple has pointed out that an Eck fistula dog with obstructed common bile ducts develops a distinct icterus, which, however, is much less intense than that observed in bile duct obstruction in a normal dog. This suggests the production of bile pigments as a true synthesis due to liver cell activity rather than a passive metamorphosis of hemoglobin pigment to bile pigment, depending solely on the supply of hemoglobin brought to the liver. An Eck fistula dog with a bile fistula puts out much less bile pigment than a simple bile fistula. The output falls sometimes to one-third normal, at times only to three-fourths normal.

"Splenectomy added to a combined bile and Eck fistula does not modify the picture nor does it change the general output of bile pigments."*

The fact that when hemoglobin is injected intravenously the output of bile pigment is increased shows that the low pigment output in Eck and bile fistula dogs cannot be explained by a faulty pigment elimination by the liver but points to a faulty or abnormally low pigment formation, and this may not be limited alone to the bile pigments. The pigment products in an Eck fistula dog are obviously much lowered, but this cannot be assumed to favor a longer life for the red cells.

At autopsy they found no definite anatomical evidence of abnormality in the hematopoietic system. The same picture was found in the bone marrow, spleen and lymph glands. The only anatomical change observed was in the liver which showed central fatty degeneration and atrophy which would point to a functionally inefficient liver. The low bile pigment output is explained as due to a lowered functional capacity of the liver.

Whipple and his associates feel very strongly that any estimate of blood destruction or of the life cycle of the red cells based upon the analysis of bile pigment or urobilin is absolutely faulty, as they have shown that diet can increase bile pigment, and liver atrophy or bile salts or bile fat can decrease bile pigment secretion with no evidence of any blood changes (anemia). They suggest that the pigment portion of the destroyed hemoglobin under certain conditions may not be quantitatively eliminated as bile pigment. An analysis of hemoglobin metabolism shows that diet may influence pigment elimination

* Whipple, G. H., and Hooper, C. W., Amer. Jour. Physiol., xlii, No. 4 (Mar., 1917).

one way, liver function influence it another way, and hemoglobin injection may cause a prompt rise in bile pigment output or a negative reaction. Therefore they do not feel that an analysis of intestinal or bile pigments can show what is happening in the liver. In anemia, bile pigment elimination may be greatly decreased during the period of acute regeneration. At times there is a fall in bile pigment output and at times a lessened elimination of bile pigment following a unit injection of hemoglobin. These results are not constant but may indicate some concentration of hemoglobin either directly or indirectly, but the maximum of this concentration is probably very complex rather than simple.

The study of pigment excretion and pigment metabolism is important in the consideration of blood diseases. As our methods for estimating these increase, undoubtedly they will become of greater usefulness in determining blood destruction. So far, the evidences of blood destruction that we can rely on are first, change in shape of erythrocytes, particularly irregular poikilocytes and small forms. These are on their way to fragmentation. Free nuclei and fragmented megacarocytes are all evidences of blood destruction. Where there is any marked destruction of red blood cells associated with hemolysis there is usually a rise in temperature; this may be accompanied by a chill and often respiratory difficulty and cyanosis. Where hemolysis is rapid, hemoglobin will be found in the urine; urobilin, urobilinogen and stercobilin in the stool are good evidence of destruction. Under normal conditions of blood destruction these are not found. As has been pointed out, the breakdown of hemoglobin is an intracellular rather than an extracellular process.

Pathologically, where blood cell destruction has progressed, iron is found deposited in the liver, spleen, kidneys and bone marrow. This process is carried on by the endothelial cells by phagocytosis, especially in the spleen. Where the spleen has been removed, the other organs, lymph nodes, bone marrow and endothelial cells share in this process, and the Kupffer cells in the liver phagocytize broken down red blood cells. The hemoglobin thus liberated is excreted by the liver as iron-free bile pigment. The iron is retained for further use, though, as has been pointed out, other tissues may take part in this hemoglobin metabolism.

Degenerative processes of the leukocytes are much harder to determine; what becomes of them is not yet clear. If one follows cases where there has been marked leukocytosis, often signs of nuclear changes, granulation, vacuolation, and changes in the protoplasm will be seen. In the leukemias also we see these same changes. A result of leukocytic breakdown is found in an increased uric acid content of the urine.

There is still less evidence of what becomes of the lymphocytes. We know that certain substances, such as benzol, radium and *x*-rays, cause a destruction of lymphocytes as well as leukocytes; but even where

they diminish rapidly in the blood following treatment by these means it is hard to recognize how they disappear or disintegrate.

In the same way, little is known of the end products of platelets. They are probably constantly lost by extravasation but in such minute quantities that there is no evidence of such extravasation.*

Lee and Robertson† have shown that repeated injections of guinea pig platelets into rabbits will produce an antiplatelet serum which will destroy the platelets of guinea pigs.

Wright and Minot‡ have described the breaking up of platelets with the liberation of prothrombin and thromboplastin. As they break up they tend to stick together and become viscous. These experiments show what the normal function of the platelets is but probably not how they disintegrate in the circulation; of this at the present we know little.

CONSIDERATION OF THE FACTORS ENTERING INTO COAGULATION

Coagulation may be defined as the colloidal change which occurs under the influence of calcium electrolytes, during which change the blood is transformed from the fluid state into the solidified state which we recognize as coagulated blood. The changes which take place during this process are now more clearly understood because the various factors which enter into them have been made capable of separate analysis. However, not all the factors which enter into the normal coagulation of blood are clearly understood, and there are today various theories as to the factors entering into the process of coagulation.

In this country, the theory of Howell§ probably represents the most widely accepted theory of coagulation. According to Howell's conception, there are five factors entering into normal coagulation of the blood: Prothrombin, antithrombin, thromboplastin, fibrinogen, and calcium. Thromboplastin alone is the only factor not present in normal circulating blood. The factors prothrombin and antithrombin are held in combination so that intravascular clotting is prevented. When blood leaves the vessels, antithrombin becomes neutralized by the thromboplastic substance, the tissue juices, and also by the thromboplastic substance given off by the platelets. The prothrombin thus liberated becomes activated by calcium, and the thrombin which results from the union of prothrombin and calcium unites with fibrinogen to form the clot.

Another theory, that of Bordet and Delange,‖ is somewhat different. In this theory, the main factors entering into normal coagulation are

* Duke, W. W., Arch. Int. Med., xi (1913), p. 100.

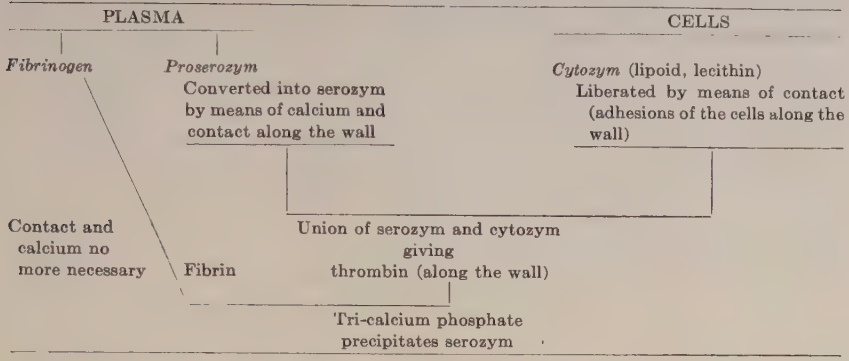
† Lee, R. I., and Robertson, O. H., Jour. Med. Research, xxviii (1915–16), p. 323.

‡ Wright, J. H., and Minot, G. R., Jour. Exper. Med., xxvi (1917), p. 395.

§ Howell, W. H., The Harvey Lectures (1916–1917).

‖ Bordet, J., and Delange, L., La coagulation du sang et la gènese de la thrombin, Ann. de l'Inst. Pasteur, xxvi (1912), pp. 657 and 738; *Ibid.*, Sur la nature du cytozyme, recherches sur la coagulation du sang, xxvii (1913), p. 341.

COAGULATION OF BLOOD ACCORDING TO BORDET'S THEORY


PLASMA
CELLS
Fibrinogen
Proserozym
Converted into serozym by means of calcium and contact along the wall
Cytozym (lipoid, lecithin)
Liberated by means of contact (adhesions of the cells along the wall)
Contact and calcium no more necessary
Fibrin
Union of serozym and cytozym giving thrombin (along the wall)
Tri-calcium phosphate precipitates serozym

EXAMPLES: Two tubes containing oxalated plasma without fibrinogen and almost devoid of cytozym (*i.e.*, platelet free).

TUBE I	TUBE II
Addition of calcium and cytozym	Addition of calcium only; after one or two hours, addition of cytozym
↓	↓
Thrombin appears only in one-half hour, the conversion of proserozym into serozym requiring time	Thrombin appears instantly, proserozym being already converted into serozym (*i.e.*, role of glass contact)

fibrinogen, which is contained in the plasma, and proserozym, which is converted into serozym by means of calcium and contact. The cells contain the coagulating factor cytozym which is a form of lipoid or lecithin liberated by means of contact (observation of cells along the wall). The union of serozym and cytozym gives thrombin which unites with fibrinogen to form fibrin and this produces clotting. In the theory of Bordet and Delange, contact along the walls of a foreign vessel, such as a test tube, is an important factor in producing coagulation because, as they have shown, if the test tubes are lined by paraffin and the blood is taken directly from the veins either through a paraffin coated needle or directly from the vein without contact, the blood does not clot. Cytozym is contained mainly in the platelets and body tissues or cells.

In Bordet and Delange's theory, coagulation of normal blood may be divided into three stages. Of the first, very little is known except that certain definite changes take place during a very short period of time. The second step, which is the formation of thrombin, depends upon the reaction between two substances which they term cytozym and serozym, acting in the presence of calcium salts to form thrombin which in turn during the third stage combines with fibrinogen to form the fibrin clot.

Bordet* gives as examples two tests which show the second and third stages. Take two test tubes containing oxylated plasma without

*Bordet, J., Hitchcock Lectures, University of California (1920).

fibrinogen and almost devoid of cytozym (that is, platelet free). To tube No. 1 add calcium and cytozym. Thrombin appears only in one-half hour. The conversion, therefore, of proserozym into serozym requires time. To the second test tube containing another portion of the same oxylated plasma, first calcium only is added. After one or two hours cytozym is added. Thrombin appears instantly, prothrombin already having been converted into serozym. This demonstrates the rôle of contact in the production of serozym in the presence of calcium. This theory does away for the most part with antithrombin as a normal factor in coagulation. Bordet thinks that antithrombin is probably present and perhaps plays a rôle in the first step but does not think it is an important factor in keeping the blood fluid in the vessels. However, it undoubtedly enters into the problem under pathological conditions.

Morawitz's* theory differs from that of Howell in the main as to the manner in which thrombin is formed. He terms the precursor of thrombin, thrombogen. Thrombogen needs the action of a kinase before it becomes active and this Morawitz terms thrombokinase which is obtained from the tissue juices and blood platelets. Morawitz does not consider antithrombin as an essential factor, though he admits its presence and considers that it is loosely bound with the thrombogen, but his thrombokinase acts directly on thrombogen instead of uniting with the antithrombin as thromboplastin does in Howell's theory. Calcium and fibrinogen are the same in Morawitz's theory as in Howell's, and the formation of the clot by the union of thrombin and fibrinogen is also the same.

Cytozym is in a rough way comparable to Howell's thromboplastic substance and to Morawitz's thrombokinase. Serozym may be considered as comparable to Howell's prothrombin and Morawitz's thrombogen, though it is not supposed to be present as such in the circulating blood or in the oxylated plasma.

Further Discussion of Factors Entering into Coagulation. Calcium.—Calcium salts, principally the chlorids, are present in the blood in the proportion of about 0.8 per cent. It is rarely diminished in blood except in conditions in which there is an excess of bile pigment in the blood, in which condition it is found to be taken up in a fairly firm combination with the bile pigment. In such instances an analysis of the blood does not show a diminution of the calcium salts, for the reason that the amount of calcium is not diminished but its availability for coagulation alone is diminished. In fact an analysis may show an increase in the calcium, calcium having been withdrawn from other tissues.† Lee and Vincent‡ have suggested a simple test which from a clinical standpoint gives a fairly accurate idea of the availability of

* Morawitz, P., Deutsch. Arch. f. klin. Med., lxxix (1904), p. 215; Arch. f. exper. Path. u. Pharmakol., vi (1906–7), p. 115; Bergmann, J. F., Ergebn. d. Physiol, Wiesbaden, iv (1905), p. 307.

† King, J. H., and Stewart, H. A., Jour. Exper. Med., xi (1909), p. 673.

‡ Lee, R. I., and Vincent, B., Arch. Int. Med., xvi (1915), p. 59.

calcium, which is more important in coagulation than the actual amount of calcium present in the blood. The test is carried out by contrasting the coagulation time of two specimens of blood, one in the usual way and one with the addition of three drops of a 1 per cent. solution of calcium chlorid. They call this test the "calcium in vitro" test. By this test they have been able to show that the delayed coagulation time in obstructive jaundice without apparent disturbance of liver function is markedly affected by the addition of this amount of calcium, whereas normal blood and other bloods with delayed coagulation due to some other factor than the calcium are not so affected.

Fibrinogen.—This is a globulin-like substance which occurs in the proportion of 0.2 to 0.8 gm. per 100 c.c. of plasma. It forms the main bulk of the clot. Whipple* has very clearly shown that its diminution is invariably associated with liver conditions especially in chronic cirrhosis. In this condition, the blood will clot in the normal time, but the clot is more or less flabby or flimsy, depending on the quantitative defect in the fibrinogen. Fibrinogen may be artificially reduced to a very low level by phosphorus or chloroform poisoning, both of which affect the liver. In most of these artificially produced conditions which affect the liver, especially those producing liver necrosis, there is a marked increase in the antithrombin content which probably plays a greater part in the disturbed coagulability of the blood than does the lack of fibrinogen. However, in the cases where fibrinogen alone is disturbed, continued bleeding may occur, due to the fact that the coagulum is not tough enough to seal the ends of the broken vessels, notwithstanding the fact that the number of platelets and the other factors are present in normal quantity.

Thromboplastic Substance. Thromboplastin, Thrombokinase or Cytozym.—This substance does not exist as such in the circulation but comes into play at the time when coagulation starts. It is synonymous with blood platelets, leukocytes and tissue juices in its action; at least it is in part derived from blood platelets, leukocytes and tissue juices. Whether it exists separately from these factors has not so far been definitely proved. It is probably not a kinase in the true sense, as Morawitz considered it to be, because in the first place it resists heat, even boiling; and in the second place, it differs from a true kinase in that it is quantitatively effective and is used up in its combination with antithrombin. The cytozym of Bordet and Delange is rather a complex substance; but as according to them it is derived directly from blood platelets, leukocytes and tissue juice, it must be comparable to thromboplastin. In all the recognized theories, blood platelets play the largest part in the production of this thromboplastic substance, and the tissue juices are the next most important source of its production.

Blood Platelets.—Wright† has clearly shown that the blood platelets are derived from the bone marrow megacaryocytes. Wright,

* Whipple, G. H., Fibrinogen, Amer. Jour. Physiol., xxxiii (1914), p. 50.

† Wright, J. H., Virchow's Arch. f. path. Anat., clxxxvi (1906), p. 55; Jour. Morphology, xxi (1910), p. 263.

Hayem and others* have shown that they are broken off from the megacaryocytes, but in just what manner they first enter the circulation is not clear. They vary in size, averaging about 3 mu. in diameter. They are usually disc shaped with a hyaline ground appearance, with somewhat darker center containing one or more granules. They are supposed to have ameboid movement† and, as shown very clearly by Duke,‡ have a very sticky consistency which causes them to clot very rapidly. There is a very definite parallel between the number of platelets in circulation and the bone marrow findings as regards the megacaryocytes.§ Blood platelets can be counted either by Pratt's method of making a careful blood smear before coagulation has occurred and staining with Wright's and Kinnicutt's solution, which is a solution of 1 to 300 brilliant cresyl blue mixed with 1 to 1000 potassium cyanide freshly prepared and mixed and filtered just at the time that the count is to be made. The count is made in the usual counting chamber. Under normal conditions, the blood platelets vary from 200,000 to 400,000 per centimeter, averaging about 250,000.

The blood platelets represent the activities of one particular cellular element of the blood-forming organs, the megacaryocyte of the bone marrow. Therefore an increase in their number must be due either to the fact that (1) the megacaryocytes are producing a larger number of platelets than normal, or that (2) the megacaryocytes themselves are increased above the normal and are (3) simply producing the normal number of platelets but due to some specific stimulation the megacaryocytes are giving off the platelets earlier than normal. In this latter condition the blood platelets might be expected to vary in size and shape, and this has actually been noted by several workers as occurring in chronic myelogenous leukemia during which there is some specific stimulation to the bone marrow.

Certain bacterial toxins are capable of increasing the number of platelets, presumably due to some stimulation of the megacaryocytes. The bone marrow, when it is stimulated by appropriate doses of x-ray, is also found to increase the number of blood platelets. During certain chronic infections, such as tuberculosis, and in certain stages of secondary anemia, the platelets are increased. Under the stimulation of high altitude and direct sunlight, both of which cause an increased activity of blood-forming organs, an increase in the platelets is found. The blood platelets are always increased after severe hemorrhage and after splenectomy performed during pernicious anemia or other diseases of the blood-forming organs. Under certain physiological

* Wright, references as above; Hayem, G., Du sang et de ses alterations, anatomiques, Paris (1889); Leçons sur les maladies du sang, Paris (1900).

† Deetjen, H., Ztschr. f. physiol. Chem., lxiii (1909), p. 1.

‡ Duke, W. W., Jour. Exper. Med., xiv (1911), p. 265; Arch. Int. Med., x (1912), p. 445.

§ Wright's and Bunting's studies. Wright as above; Bunting, C. H., Jour. Exper. Med., xi (1909), p. 541.

conditions blood platelets are found to be increased, as during menstruation and pregnancy. The post-mortem study of the bone marrow, spleen, and liver of chronic myelogenous leukemia shows that there is an enormous increase in the number of the megacaryocytes, which corresponds with the enormous increase in the number of blood platelets found in this condition. Under certain conditions of general hypersensitization, such as anaphylaxis, there is an increase in the number of platelets.

On the other hand, in conditions which diminish the activity of the megacaryocytes or completely destroy them, we find a constant diminution in the platelets. During the course of most acute infections, such as typhoid fever, there is more or less of a decline in the number of platelets, which may fall to such a low level that purpuric or hemorrhagic symptoms appear. These hemorrhagic conditions which are seen in certain acute infectious diseases must, however, be sharply differentiated from those much more serious hemorrhagic conditions which occur during certain septicemias, in which the underlying factor which is disturbed is not the platelet but rather the antithrombin factor. During acute benzol poisoning there is a rapid diminution, almost a disappearance, of the blood platelets. I have seen the blood platelets in a case of myelogenous leukemia diminish from 1,120,000 per centimeter. to a point where no blood platelets practically could be made out during an acute and fatal benzol poisoning, showing the wide fluctuation which these cells are capable of undergoing depending on whether the bone marrow is being stimulated or destroyed. Under prolonged or excessive doses of *x*-ray there is a marked diminution of the platelet count. The diminution in lymphatic leukemia, in aplastic and pernicious anemia, and other anemias furnishes an excellent criterion for the disease. A diminution always shows that the bone marrow is being seriously disturbed as to its functional activity, so that platelet counts may be considered of prognostic value as well as an indicator as to whether the treatment should be diminished or intensified.

Whether the blood platelets are destroyed in the circulation in certain conditions which do not affect the bone marrow is not certain. The fact that Lee and Robertson* were able to produce an anti-blood platelet serum of high potency which destroyed the blood platelets without affecting the megacaryocytes does not necessarily indicate that such conditions occur, but it is certainly suggestive. What becomes of the blood platelets is not known. Duke and others† have shown that the life of the blood platelet is approximately four days, which is a very much shorter period than that of the other cellular elements of the blood. Whether the blood platelets are taken up by the tissues and furnish the tissues with most of their thromboplastic

* Lee, R. I., and Robertson, O. H., Jour. Med. Research, xxviii (1915–16), p. 323.

† Duke, W. W., Jour. Exper. Med., xiv (1911), p. 265; Arch. Int. Med., x (1912), p. 445.

substance is not clear. Lee and Minot* believe this to be the case.

The technique involved in obtaining blood platelets in an unchanged state is very difficult. They can be obtained in an almost unchanged state by proper technique, both from the buffy coat and by re-centrifugalization of the cloudy plasma. A microscopical study of the changes which occur in the platelets as they first begin to agglutinate seems to indicate that they are of a colloidal nature, the platelets becoming fused and changing from their granular, living appearance into glassy-like masses as coagulation progresses. This is undoubtedly due to a rearrangement of the various protein molecules, and during clot formation these changes in the platelets are accompanied by the first appearance of the fibrin shreds from the fibrinogen.

The active principle in the platelets is soluble both in strong saline solution and in distilled water; and its active principle, as also the active principle of tissue juices, can be subjected to considerable heat without affecting its activity in promoting coagulation.

The blood platelets not only enter into the first steps of coagulation, but the active principle is involved in the retraction of the clot. Of course, the retractility of the clot may be affected by a defective quantity of fibrinogen or by an excess of antithrombin. According to almost all the workers who have studied this phase of the problem, the platelets which are not used in coagulation go into solution. This solution is active in the production of clot retraction, so that the phenomenon of clot retraction is another valuable indication of the presence of abundantly active platelets. A normal coagulation time with a delayed or absent retractility of the clot would indicate a quantitative rather than a qualitative defect in the platelets. On the other hand, a prolonged coagulation time with a normal clot retraction might, according to Lee *et al.*, indicate that the platelets had a qualitative rather than a quantitative disturbance if all the other factors in the blood were normal. The condition in which the diminution of platelets is most constantly found is that of purpura hemorrhagica which will be discussed later.

Prothrombin.—Prothrombin (Howell) and thrombogen (Morawitz) are supposed to be present in the circulating blood as such. According to Bordet, however, the serozym is not present as such in the blood but makes its appearance just at the time when coagulation begins. It is supposed to be derived from the platelets but its absolute source is not definitely known. Howell demonstrates its presence by oxalating the blood, which fixes the platelets, then centrifugalizing and recalcifying by the addition of the optimum amount of calcium chlorid. The coagulation time is then measured by the invertibility of the clot, the normal time being from 6 to 12 minutes. The prothrombin quotient or factor is obtained by dividing the coagulation time of the specimen of plasma containing the optimum amount of calcium, by

* Lee, R. I., and Minot, G. R., Arch. Int. Med., xviii (1916), p. 474; Cleve. Med. Jour., xvi, (Feb., 1917), p. 65.

the coagulation time of the normal blood tested at the same time, under the same conditions, and by the same method. Prothrombin may be obtained pure by Howell's method. Howell feels that this is a quantitative test for prothrombin, and by its use has shown a markedly delayed coagulation time on recalcification in cases of hemophilia. This has also been shown by Whipple, Hurwitz and Fonio.* On the other hand, Lee *et al.*,† feel that the important factor in hemophilia is the qualitative change in the platelets.

Antithrombin.—According to Howell, antithrombin is an essential factor when present in its normal amount in keeping the circulating blood fluid. It is not present in large amounts but is present in amounts sufficient to bind the prothrombin and render it inactive. Antithrombin is a substance which is very resistant to heat, i.e., it is not destroyed by boiling and is capable of diffusion. Herudin or leech extract is composed almost entirely of antithrombin; it can be obtained in fairly pure state by autolysis of such organs as the liver. When peptone is injected intravenously, through its stimulation of the liver antithrombin is produced in large amounts. Whipple‡ has shown very clearly that the liver is the essential organ for its production, and that in conditions which seriously affect the functionating power of the liver, antithrombin is found in great excess. When this occurs, purpura and hemorrhagic conditions usually appear. Whipple has shown this to be particularly true in conditions which produce liver necrosis, such as occur during cancer growth of the liver. He has shown it to be present also in several cases of septicemia, as well as in certain anemias which he has studied, such as leukemia and aplastic anemia. Whipple feels that the antithrombin factor is very often affected and that there are many conditions in which the over production of antithrombin is due to the over stimulation of the liver. In obstructive jaundice, even where there is quite a reduction in the available calcium, hemorrhage does not appear unless some other factor, usually the antithrombin, is affected. It is this disturbance of the antithrombin-prothrombin balance which we feel is the most important factor in most of the hemorrhagic conditions and explains most satisfactorily the various conditions in which these two factors are found disturbed.

When the antithrombin is very markedly diminished, we have a condition in which thrombus formation is very easily produced; it needs but the slightest abrasion or perhaps even a change in the rate of the flow of blood to allow the action of prothrombin with calcium to form thrombin and so produce the thrombi which are found in cases of spontaneous thrombosis as well as those which occur during certain

* Whipple, G. H., Arch. Int. Med., xii (1913), p. 637; Hurwitz, S. H., Amer. Jour. Med. Sciences, cliv (1917), p. 689; Fonio, A., Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, xxviii (1914), p. 642; and Deutsch. Med. Woch., xlii (1916), p. 1344.

† Arch. Int. Med., xviii (1916), p. 474.

‡ Whipple, G. H., Hemorrhagic Diseases, Antithrombin and Prothrombin Factors, Arch. Int. Med., xii (1913), p. 637.

infectious conditions. That there are waves of depression and stimulation in the formation of antithrombin there can be very little doubt. Howell* has shown that, in these cases of spontaneous thrombosis, there is a diminution of antithrombin with the other factors normal. Whipple and Hurwitz† as well as other workers in this field have pointed out that the same stimulus may be able to produce at one time an excess of antithrombin and at another a diminution way below the normal, depending somewhat on the condition of the liver. In septicemias this antithrombin content is much increased. Whipple and Lucas‡ have shown this present in certain cases of hemorrhage of the newborn, in which streptococci were found in the blood cultures. In these cases, the platelet counts were normal, the prothrombin in normal amounts, calcium normal, and the antithrombin was found present in quantities far above the normal. These cases probably explain the negative results of transfusion in some cases of malena neonatorum. The prothrombin-antithrombin equilibrium is one of the most delicately adjusted mechanisms which has been studied, and it is probable that all the factors governing this adjustment have not been clearly demonstrated.

Howell and Holt§ have demonstrated, in their work on antithrombin substances in the blood, that there are probably two substances acting as factors in blood coagulation. The first is a phosphated substance which exists in various tissues, especially the liver, which they have termed heparin. The second substance, pro-antithrombin, is present in the plasma and serum and is the true precursor of antithrombin by a reaction with heparin which is also found normally in the circulation. These two substances together prevent intravascular clotting and the formation of thrombin in the circulation. An antithrombin solution of itself has no pure antithrombic action but will act as such when it is added to blood inside or outside the body.

Thrombin, which can be produced in a pure state by Howell's method, is seldom if ever affected in hemorrhagic conditions. The difficulty lies in the steps that go before the formation of thrombin. It is difficult to test for thrombin quantitatively; as has been shown, its precursor, prothrombin, can be tested for or demonstrated in a fairly accurate quantitative way, so that it is not necessary to consider this factor in the study of hemorrhagic conditions.

There is one other factor of significance which has neither been appreciated nor in fact been suggested as a factor entering into coagulation until Hess‖ demonstrated the difference between the various protein fractions. Hess demonstrated the fact that the euglobulin fraction is the one which enters into coagulation, the other fractions

* Howell, W. H., Arch. Int. Med., xiii (1914), p. 76.

† References as above.

‡ Whipple, G. H., Arch. Int. Med., ix (1912), p. 365; Lucas, W. P., *et al.*, Blood Studies in New-born, Am. J. Dis. Child., XX (1921) p. 525.

§ Howell, W. H., and Holt, E., Two New Factors in Blood Coagulation—Heparin and Pro-antithrombin, Amer. Jour. Physiol., xlvii (1918), p. 328.

‖ Hess, A. F., Proc. for the Soc. Exper. Biol. and Med., xiii (1915), p. 125.

apparently taking no part in this process. This is certainly a most significant and interesting finding and opens a new field for investigation in the hemorrhagic diseases and introduces a new factor into the consideration of the coagulation of the blood.

Determination of Coagulation Time.—This means the time that blood drawn into a clean test tube (the best size is from 15 to 25 mm. in diameter) takes to clot so that the test tube can be inverted without the clot slipping. The blood for coagulation time should be taken directly from a vein, in order that the tissue juices may not enter it, for the tissue juices themselves are important factors in aiding coagulation. The blood should be drawn from the longitudinal sinus in infants. Care should be taken that no damage is done to the tissues on entering, because this in itself will make the test entirely unreliable. The test tubes should be scrupulously clean. If a syringe is to be used, it should be coated with paraffin or with petrolatum ether mixture. The time should be taken from the moment blood first appears. One to 2 c.c. should be put into three or four separate test tubes (21 mm. in diameter). At minute intervals the test tubes should be tilted gently. It is best to examine the test tubes separately on alternate minutes, for the coagulation time will be decreased the more the test tubes are manipulated. When the test tubes can be inverted without the clot slipping, this is to be regarded as the coagulation time. By this method, the coagulation time of normal blood averages from 6 to 12 minutes; anything over 20 minutes we have taken as meaning definitely delayed coagulation. It is best when examining supposedly pathological blood to take for comparison a normal blood at the same time and under the same conditions.

Determination of Bleeding Time.—Determination of bleeding time is estimated by making a fresh cut, preferably with a scalpel, in the finger or lobe of the ear, so that the blood flows drop by drop. The blood is taken up on absorbent paper (laboratory filter paper or blotting paper may be used) at intervals of 30 seconds. In this way, each drop will give the amount of blood shed in a given interval, and the total duration from such a bleeding point will be the bleeding time. Bleeding time varies in a normal individual from one to three minutes and is independent of the coagulation time. The bleeding time gives information not only in regard to the factors circulating in the blood but also as to the condition of the tissue juices, the elasticity of the skin, and particularly it gives us information regarding the blood platelets. Bleeding time and coagulation time may not necessarily be the same; bleeding time may be normal when the coagulation time is delayed, or *vice versa*. Bleeding time is of considerable importance from a diagnostic point of view. It should be tested before operating in cases where there is a tendency to bleed (hemophilia).

Retractility of the Clot and Enumeration of Blood Platelets. Immediately after the coagulation time of the blood has been taken in the original test tube, have this put into an incubator at 37°C. from 12 to 24 hours. It will be found that the clot retracts, at the

same time expressing serum. Normally this retraction begins within a few hours and is complete within 18 to 24 hours. In certain pathological conditions, retraction may not occur at all or be very markedly delayed. The blood platelets should be counted by the Wright and Kinnicutt* method of staining. The technique of this is as follows: A solution of 1 to 300 brilliant cresyl blue is mixed with a freshly prepared solution of potassium cyanide, 1 to 1000, and filtered just at the time that the count is to be made. The count is made in the usual counting chamber (red cell counting pipette, blood taken up to 0.1 mm.). Under normal conditions blood platelets vary from 200 to 400 per centimeter, averaging about 250. As has been stated, the blood platelets represent the activity of the megacaryocytes of the bone marrow and give us a very good indication of the activity of this important factor of the blood-forming organ.

Prothrombin.—The amount of prothrombin present in the blood may be estimated by Howell's method.† Oxylated plasma (that is, one part of 1 per cent. solution of sodium oxalate made up in 0.9 per cent. solution of sodium chlorid to nine parts of blood) is put in a series of small test tubes, ½ to 1 c.c. in each test tube. To each of these test tubes in order is added dilute calcium chlorid (0.5 per cent.), one drop to the first, two drops to the second, three drops to the third, and four drops to the fourth. Usually four test tubes are enough for this test, coagulation being determined by the invertibility of the clot. The normal clotting time will average about 10 minutes; whereas if the prothrombin element is diminished, it may be delayed or not appear at all. This is a very good test to estimate the activity of the platelets, as they are the chief cells from which prothrombin is derived. It is a very good test for hemophilia and purpura hemorrhagica, in which conditions the prothrombin factor is deficient or partially inactive, or the platelets are diminished.

Fibrinogen and Calcium.—It is difficult to determine by any simple means the fibrinogen content of the blood. A rough measure of the fibrinogen content, however, can be made by examining the blood clots in the small test tubes, especially those to which oxalated plasma was added and coagulation produced by calcium. The calcium factor cannot easily be directly determined. It has, however, been found less often deranged, except in those cases connected with icterus, in which condition the calcium is not actually diminished but is in combination with the bile pigments and therefore not available rapidly for coagulation. A rough estimate of the calcium may be obtained by the method described by Lee and Vincent‡ as the "calcium in vitro" test in which a series of test tubes are similarly prepared as for coagulation time, 2 c.c. of blood being added to each and three drops of calcium chlorid, 1 per cent. solution. The addition of this amount of calcium will accelerate the clotting of blood from cases of

* Wright, J. H., and Kinnicutt, R., Jour. A. M. A., lvi (1911), p. 1457.
† Howell, W. H., Amer. Jour. Physiol., xxxv (1914), p. 474.
‡ Lee, R. I., and Vincent, B., Arch. Int. Med., xvi (1915), p. 59.

obstructive jaundice, for instance, but will not influence coagulation time of normal blood.

Fibrinolysis.—Under certain pathological conditions, after the clot has formed in the normal time it is found that oozing continues and the clot is softened or dissolves and bleeding continues—the same process, coagulation followed by softening of the clot, being repeated over and over again. Under such conditions it was found that a fibrinolytic ferment was present. This can be detected by incubating a clot at 37°C. Normally the clot will not soften within 24 hours; under pathological conditions, complete softening or disappearance of the clot occurs within 12 hours.

CONSIDERATION OF SOME OF THE PHYSIOLOGICAL AND CHEMICAL ASPECTS OF THE BLOOD

We have so far confined ourselves to a discussion of the blood on morphological lines, considering the cellular elements, their normal formation, and the conditions under which there may be depression of the blood-forming organs or destruction of the cellular elements. We have also considered some of the other factors, such as blood volume and coagulation, as far as we have a clear understanding of these factors.

At the present time there is a great deal of work being done in studying the blood by chemical methods. The impetus of this work rests on the introduction by Folin* of the microchemical methods of studying small samples of blood, and almost every week new methods of study are being brought out. There will be no attempt made to describe the various methods; but some of the results of these studies and their application to a better understanding of disease should be considered if we are to consider the blood as a tissue which is capable of very intensive investigation which will aid materially in a better comprehension of normal and diseased conditions, not only those connected with the blood itself or blood diseases but also disease as it affects other organs.

The study of the blood proteins, serum albumin and globulin; determination of the non-protein nitrogen with its components, urea, creatinin, uric acid, amino acids and ammonia; the study of the lipoid constituents, fat, lecithin and cholesterol; the study of salts, especially the chlorids, calcium, phosphates, magnesium, potassium and iron; the study of the blood gases, carbon dioxide and oxygen, and the estimation of hydrogen-ion concentration of the blood; the detection of acetone and phenol and the blood enzymes, as diastase and catylase, all need careful consideration when investigations of the blood are to be made. They may serve to clarify many conditions and aid in the diagnosis, prognosis and treatment not only of blood diseases but

* Folin, O., Amer. Jour. Physiol., xiii (1905), pp. 45, 66, 117; Harvey Lectures (1920); Jour. Biol. Chem., xvii (1914), p. 475; and Folin, O., and Denis, W., Jour. Biol. Chem., xvii (1914), p. 487.

also of such conditions as nephritis, diabetes, tetany, rickets and acidosis, etc.

Slemons* has lately thrown a great deal of light on the problem of the nutrition of the fetus by studying the maternal and fetal blood. All the studies of the placenta and the circulating blood of the mother and fetus show that there is no direct interchange. Certain substances pass in one direction while others pass in the opposite direction, but all traverse the same placental partition which consists, at least in the latter half of pregnancy, of a thin covering of epithelium and a layer of connective tissue and within this the delicate wall of the fetal capillary system. How substances pass through this partition has been the subject of two main hypotheses.

First, the vitalistic hypothesis in which it is held that the placenta actually digests the food of the fetus. This was first suggested by William Harvey, and Hofbauer strengthened this theory by demonstrating the presence of enzymes in the placenta, though it was never shown that these lipolytic, diastatic and proteolytic enzymes are agents in the placental interchange. Murlin in his Harvey Lecture, 1917, concluded that the vitalistic theory was probably the correct one.

The second theory is the mechanistic hypothesis which holds that the placental partition plays a passive role and behaves as a semi-permeable membrane. Cohnstein and Zuntz have shown that oxygen and carbon dioxide pass equally well from mother to fetus or in the opposite direction. They also pass from the point of higher to that of lower concentration. The loss of diffusion holds true for the placental transmission of anesthetics, chloroform, ether, nitrous oxide, though they do not apply to gases like carbon monoxide which enter into chemical combination with the hemoglobin. They also showed that sodium chlorid passed the placenta by osmosis, as also glucose.

Gusserow has shown that no insoluble substance can pass the placenta if it is normal. Thus cinnabar, barium sulphate and other insoluble compounds are effectually confined within the circulation into which they are injected. Kehrer found that many poisonous substances pass the placenta; 43 out of 73 on examination did so. Thus strychnia, hydrocyanic acid, nicotin, curare, pilocarpin, physostigmin, phlorrhizin, sodium sulphate, methylene blue and epinephrin have been demonstrated in the mother after they have been injected into the fetus. On the other hand, when a mother is suffering from leukemia, the infant will present a normal blood picture.

Slemons and his coworkers investigated data relative to organic foodstuffs, protein, carbohydrate and fats. Protein, after being broken down into simpler nitrogenous compounds, the amino acids, is absorbed into the blood stream, being used for construction and repair. In this process there are certain waste products which are much smaller in structure than proteins, though like them they have nitrogen in their

* Slemons, J. M., Transactions of Amer. Gynecological Society, xliv (1919), p. 113.

molecules. The blood contains certain well known proteins and a number of nitrogenous substances. The blood protein may be considered as reserve material, and the non-protein compounds as those which are being used in the nitrogenous metabolism. The non-protein nitrogen in mothers averaged 25.2 mg. of non-protein nitrogen per 100 c.c. of blood and the fetus 24.9 mg. This indicates that non-protein nitrogen passes freely through the placental partition. There is some evidence of the regulatory mechanism which maintains the same concentration of non-protein nitrogen in the two circulations, which is best explained on the basis that it is a simple diffusion which allows the ready passage of certain substances through a semi-permeable membrane, thus securing equal concentration on both sides of the partition.

Slemons and his associates studied amino acids, urea, ammonia, uric acid and creatinin. Abel has shown that amino acids pass readily through a semi-permeable membrane. The proof that amino acids supplied by the mother were the material out of which fetal proteins are constructed is a fundamental fact and changes the conception of tissue metabolism for the fetus and leaves no room for doubt regarding the elementary substance which the mother contributes to the fetus for the manufacture of its tissue proteins. We do not have to assume that the placenta synthesizes these proteins for the fetus.

Morse, using Van Slyke's method, showed that the blood corpuscles as well as the blood plasma of the fetus are richer in amino acids than those of the mother. This excess amounts to about 2 mg. This additional concentration in the fetus of amino acids indicates that there is a regulatory mechanism in the placenta in addition to simple diffusion. This phenomenon has been termed absorption by Van Slyke who found that when amino acids were injected into the circulation they diffused into the tissues rapidly, and an equilibrium between the fluids was obtained only when the tissues contained 10 times as much amino acid nitrogen as the plasma.

Waste products are generally excreted by the kidneys. This means that they must be transferred through the placenta from the fetal to the maternal circulation. Slemons found that in normal pregnancy these products appeared in equivalent concentrations on both sides of the placental partition. Urea, which is the most abundant nitrogenous waste product, is so readily diffusible that it is found in the same concentration in blood plasma, corpuscles and tissues. In 16 normal cases, Slemons found the average to be 10.5 mg. of urea per 100 c.c. of blood for the mother and 10.4 mg. for the fetus. In nephritis where there is a marked increase of urea as much was found in the maternal as in the fetal blood. Therefore, Slemons concludes that the placenta can take no part in the elimination of fetal urea. The test for creatinin gave the same figures. Ammonia as well as urea passes through the placenta by diffusion. It can, therefore, be safely concluded that the placenta plays a passive rôle in the trans-

mission of all nitrogenous fetal products and ordinarily estimation of the quantity of them in the mother's blood holds equally valid for the blood of the fetus.

Blood Sugar.—In the intermediary metabolism this is found in the form of glucose. Slemons used Benedict's method for testing this. In the mother the average was found to be 0.132 per cent., and for the fetus, 0.115 per cent. These tests show that there is no reason for assuming the presence of an enzyme, as was advocated by Hofbauer. The slightly higher maternal values promote a steady flow of sugar toward the fetus. This fact intimates that glucose plays an important role in fetal metabolism which is very intimately connected with an appreciation of the fat content of the blood. Slemons cites the case of double-ovum twins where each fetus had its own placenta. The blood sugar of one was 0.099 per cent. and of the other 0.096 per cent., while that of the mother was 0.12 per cent. Such findings can be explained only by diffusion of glucose through the placenta.

Fats and Lipoids.—Fats and lipoids are more abundant in the maternal blood and relatively large maternal values are associated with large fetal values. There is quite a disparity between the quantity of fats and lipoids in the two circulations, so that it is not possible to entertain the possibility of fats passing between the placenta in the same way as do other substances. There are two possibilities: One that fats and lipoids cross the placenta with the aid of an enzyme, or that they do not cross at all. Slemons' facts point to the latter being the true interpretation. Following the investigations of Hofbauer, Gage and Gage, Mendel and Daniels resorted to vital staining, employing sudan III. They found that injecting the dye into the maternal circulation caused the maternal fat to be stained and not the fetal. There was a sharp demarcation in the placenta. Stained fat cannot be traced in transit through the organ, so that it is clear that fat is not contributed from the maternal circulation to the fetus but that the fat in the body of the fetus is manufactured from carbohydrates. This agrees with the finding of abundant glucose in the maternal blood. This is certainly true of the latter part of pregnancy from the time when the placental partition becomes simplified in the eighteenth or twentieth week of pregnancy when rapid fetal growth begins. At least during the latter half of pregnancy the placental partition behaves as a semipermeable membrane.

Amino acids which go to the production of fetal protein, and glucose which supplies the requisite energy for tissue construction pass this membrane in the same way as water and most of the inorganic salts, calcium, magnesium sodium and potassium pass this semipermeable membrane.

Iron presents an intricate and unsolved problem but how it passes through the placenta is not clear. It is found, of course, stored in large quantities in the fetus. Bunge believes that this is in the nature of compensation for the inadequate amount of iron in the human milk.

The question of cholesterol and lecithin is an interesting and important problem yet to be solved. We can go no further than the fact of the high fat content in the blood of the pregnant woman and a much lower one in the blood of the fetus.

Slemons and Morriss* found that asphyxia dependent on impairment of the fetal heart action is attended with a notable increase in the urea of the fetal blood.

Slemons and Curtis† found that the total amount of fat and fat-like bodies varies between 600 mg. and 1200 mg. per 100 c.c. of maternal blood. The fetal determinations varied within much narrower limits, generally from 500 mg. to 700 mg., with most of the results approaching the lower figure. In the fetal blood, the total cholesterol esters were found in the fetal blood, the cholesterol being exclusively in the free form. The difference between the total cholesterol of maternal and fetal blood in cases in which delivery was effected without anesthetic is accounted for by the quantity of cholesterol esters in the maternal blood. The quantity of free cholesterol is the same in both circulations. The placental partition is permeable for free cholesterol and impermeable to cholesterol esters. The blood cholesterol estimations are of value in the clinical examinations of auto-intoxication.

Marriott and Sisson‡ found the blood fat of the newborn infants to be independent of the state of nutrition of the infant. Subcutaneous fat does not necessarily bear any relation to circulating fat. However, the infant who is gaining in weight will have a higher average blood fat than one who is not gaining, and breast fed infants who are gaining in weight have relatively high blood fat percentages.

Sedgwick and Kingsbury§ found that the uric acid content during the first few days of life in 39 cases was 3 mg. at birth, increasing to 3.9 mg. on the third day, and falling gradually to 1.6 mg. about the tenth day. They believe that there is a parallelism between the high uric acid content of the blood of the newborn and the high excretion of this substance during the first three or four days of life. The human fetal tissue, therefore, probably possesses no uricolytic power.

Sedgwick and Ziegler‖ studied the blood of newborn, breast fed infants from the age of 3 days to 43 days for the nitrogenous and sugar content of the blood. They found that the non-protein nitrogens were high in the first few days of life, being from 40.6 to 53.7 during the first week, and did not reach normal until sometime during the end of the second week. The urea nitrogen was not increased over the maximum normal value for adults. The creatin plus creatinin values

* Slemons, J. M., and Morriss, W. H., Bull. Johns Hopkins Hospital, xxvii (1916), p. 343.

† Slemons, J. M., and Curtis, C. S., Amer. Jour. Obs., lxxv (1917), p. 569.

‡ Marriott, W. McK., and Sisson, W. J., Amer. Jour. Dis. Child., xvi (1918), p. 75.

§ Sedgwick, J. P., and Kingsbury, F. B., Amer. Jour. Dis. Children, xiv (1917), p. 98.

‖ Sedgwick, J. P., and Ziegler, M. R., Amer. Jour. Dis. Child., xix (1920), p. 429.

were high, whereas the creatinin and sugar values were normal and essentially the same as adult normal values. The following table gives the average values which Sedgwick and his associates found for blood analyses of the newborn:

AVERAGE VALUES FOR BLOOD ANALYSIS (SEDGWICK AND ZIEGLER)

Age, days	Non-protein nitrogen	Urea nitrogen	Crea-tinin	Creatin plus creatinin	Sugar, per cent.	Number of analyses on which average was made
3	53.7	16.8	1.7	8.9	0.07	4
4	46.9	17.3	1.8	6.7	0.09	4
5	48.2	15.9	1.8	7.5	0.07	11
6	38.4	15.6	1.5	6.3	0.08	8
7	40.4	14.1	1.7	6.2	0.08	5
8	37.5	10.5	1.8	6.1	0.09	5
9	38.8	12.9	1.6	7.3	0.09	4
10	30.4	12.1	1.5	8.0	0.07	3
11	34.0	8.0	1.6	5.3	0.08	1
12	26.6	9.9	1.6	5.4	0.08	3
13	37.7	10.4	2.1	5.0	0.09	1
16	43.1	....	2.0	5.2	0.07	1
43	23.6	13.6	1.4	9.4	0.09	1

In certain nutritional conditions, nutritional diseases and infections it is important to study the blood proteins. As has already been pointed out, the total blood volume in certain of these conditions varies materially. Utheim* has studied the protein content during infancy and finds that it varies normally from 6 to 6.5 per cent. and remains at this level until the tenth or eleventh month when it begins to rise and reaches the adult normal level of 7 to 8 per cent. by the fifteenth month. The following tables illustrate the normal values for blood protein and the reduced values found in premature and athreptic infants:

* Utheim, K., Amer. Jour. Dis. Child., xx (1920), p. 366.

TABLE III.—THE BLOOD PROTEIN OF NORMAL INFANTS (UTHEIM)

Age	No. of infants examined	Average protein per-centage	Age	No. of infants examined	Average protein per-centage
1 day	14	6.25	3 months	1	6.06
2 days	12	5.8	3½ months	2	6.33
3 days	12	6.33	4 months	2	6.55
4 days	9	6.63	4½ months	3	6.35
5 days	13	6.59	5 months	4	6.90
6 days	9	6.25	5½ months	1	6.12
7 days	8	6.83	6 months	2	6.34
8 days	4	6.27	8 months	1	6.12
9 days	7	6.33	11 months	1	6.87
10 days	3	6.19	13 months	3	7.00
11 days	4	6.03	13½ months	1	7.63
12 days	4	6.26	15 months	1	7.42
13 days	3	6.47	16 months	3	7.63
14 days	3	5.90	17 months	3	7.63
16 days	1	6.12	20 months	1	8.71
1 month	3	6.29	2 years	2	7.86
1½ months	3	6.28	2⅓ years	1	8.06
2 months	2	6.32			

NOTE.—Above table taken from "A Study of the Blood and its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbances," by Kirsten Utheim, M.D., Amer. Jour. Dis. Children, xx (1920), p. 366.

TABLE IV.—BLOOD PROTEIN OF PREMATURE INFANTS (UTHEIM)

Number	Age	Average protein percentage	Number	Age	Average protein percentage
1	1 day	4.91	13	3 weeks	5.03
2	1 day	4.16	14	5 weeks	4.16
3	2 days	3.94	15	5 weeks	5.42
4	3 days	5.13	16	6 weeks	4.47
5	3 days	5.13	17	6 weeks	4.42
6	1 week	5.78	18	7 weeks	5.03
7	2 weeks	5.05	19	7 weeks	5.23
8	2 weeks	5.68	20	9 weeks	5.68
9	2 weeks	5.68	21	10 weeks	5.90
10	3 weeks	4.59	22	3 months	6.34
11	3 weeks	4.49	23	3¼ months	6.77
12	3 weeks	4.26			

NOTE.—Taken from "A Study of the Blood and its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbances," by Kirsten Utheim, M.D., Amer. Jour. Dis. Children, xx (1920), p. 366.

TABLE V.—BLOOD PROTEIN OF ATHREPTIC INFANTS (UTHEIM)

Number	Age, months	Protein percentage	Number	Age, months	Protein percentage
1	1	5.78	20	3	5.68
2	1	5.13	21	3	5.47
3	1	5.30	22	4	5.31
4	1½	4.59	23	4	5.90
5	1½	5.68	24	4	5.57
6	1½	5.57	25	4	5.90
7	1½	5.38	26	4½	5.57
8	2	4.37	27	4½	5.49
9	2	5.68	28	4½	5.30
10	2	5.31	29	5	5.47
11	2	5.90	30	5	5.25
12	2	4.69	31	5½	5.80
13	2½	4.69	32	5½	5.57
14	2½	4.59	33	6	5.25
15	2½	4.81	34	6	4.67
16	3	5.78	35	7	5.32
17	3	4.91	36	9	6.16
18	3	5.68	37	18	3.94
19	3	5.78			

NOTE.—Taken from "A Study of the Blood and its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbances," by Kirsten Utheim, M.D., Amer. Jour. Dis. Child., xx (1920), p. 366.

Due to the concentration of the blood, the blood protein is markedly increased in diarrheal conditions and ranges from 8 to 9+ per cent.

Whipple and his associates* have studied the effect of blood serum protein regeneration under various conditions of depletion and intoxication. They found that when the serum protein is depleted to 1 per cent. this appears to be the absolute minimum below which the body cells cannot survive. Many of their experimental animals would not survive a depletion to 2 per cent. This agrees very well with Utheim's findings in athreptic infants. They also call attention to the fact that the body regenerates the cell protoplasm with considerable difficulty and shows delay following cell injury. Whipple has pointed this out in relation to liver injury by chloroform poisoning where the repair of damaged cell protoplasm takes from 7 to 10 days, depending upon the severity of the original cell necrosis. They point out the similarity between the parenchymatous regeneration and the blood serum protein regeneration and suggest that it may very well be that the protein for the parenchyma cells or the blood plasma may require similar construction periods and building material, and it may be that the blood protein construction depends on the activity of the cell protein. It is possible, they conclude, that all protein material may be built up

* Amer. Jour. Physiol., xlvii (1918), pp. 356 and 370.

partly alike, to be differentiated in the last stage of the complete elaboration.

They found regenerative power to be about 1 per cent. total protein during the first 24 hours following plasmapheresis. They found that this percentage was remarkably constant and did not seem to be influenced by diet or fasting, nor was it influenced by shock, so that this can be looked upon as the maximum effort of the body to replace the essential serum proteins, an effort which depends on the body protein as it is present in fasting experiments. It is the same whether there is a great increase in the breakdown of host protein, as evidenced by great increase of urinary nitrogen, or whether this tissue autolysis is minimal.

These experiments are very suggestive for future study and should throw much light both on the prognosis in nutritional conditions and also on the progress of the condition if the proteins can be followed for their regeneration or lack of regeneration.

Hurwitz and Meyer* studied the serum globulins in bacterial infections and their relation to immunity. They conclude that:

"The progress of an infection is usually associated with marked changes in the serum proteins. There may be an increase in the percentage of the total protein during some stage of the infection, and there is usually a change in the albumin-globulin ratio with an increase in the total globulins. This rise may antedate the development of any resistance by a considerable period of time.

"The non-protein constituents of the blood show fluctuations with a tendency to rise as the infection progresses.

"The process of immunization is in almost all instances associated with a definite increase in the globulins of the blood, and in some cases with a complete inversion of the normal albumin-globulin ratio. This may be produced both by living and dead organisms and by bacterial endotoxins. Massive doses usually result in an upset which shows no tendency to right itself during the period of observation. . . .

"Animals possessing a basic immunity show a more rapid rise in the globulin curve following inoculation.

"There is no parallelism between the leukocytic reaction and the globulin reaction. During periods of leukopenia the globulins may be as high as during the period of a leukocytosis."

The Schmidts† working on the chemical nature of the immune bodies in relation to changes in the protein quotient produced by the injection of toxins, killed cultures, or by infection with a living organism, conclude that a rise of globulins is not necessary for immune body production.

This agrees with the work of Whipple and Cooke‡ who studied proteose intoxications and injury of body protein. They showed that

* Hurwitz, S. H., and Meyer, K. F., Jour. Exper. Med., xxiv (1916), p. 515.

† Schmidt, E. S., and Schmidt, C. L. A., Jour. of Immunology, ii No. 4 (1917), p. 343.

‡ Whipple, G. H., and Cooke, J. V., Jour. Exper. Med., xxv, No. 3 (1917), p. 461.

the "non-protein nitrogen of the blood may show a considerable increase above normal due to intestinal obstruction or the presence of a closed intestinal loop. A definite rise in blood non-protein nitrogen may be found in association with general peritonitis or septicemia, and an acute rise can be demonstrated following an injection of a toxic proteose."

They repeatedly observed an increase of over 100 per cent. non-protein nitrogen in the blood within three or four hours following an intravenous injection of 100 mg. to 300 mg. of purified proteose obtained from closed intestinal loops. Such a retention cannot be accounted for by any kidney retention of non-protein nitrogen, and they suggest that there is a marked protein or tissue disintegration associated with proteose intoxications. The apex of this rise occurs during the second 24-hour period and takes from three to five days before it reaches its original base line. They conclude that this "speaks for a definite cell injury with destruction of considerable protein substance," and the "disturbance of cell equilibrium is not rapidly or promptly restored to normal."

There is a marked rise in the urinary nitrogen output, which indicates a considerable breakdown of the body proteins, and they believe that the destruction of protein is an important part of the intoxication, which also explains the rise of non-protein nitrogen in the blood. As immunity to this proteose intoxication develops, there is a fall in the nitrogen curve toward normal. During the intoxication there is a definite diuresis, though this is often masked by the increase in vomiting in the obstruction experiments. With this there is marked increase in thirst. The body proteins during acute proteose intoxication take up water from the blood, and if recovery takes place, this excess of water will be thrown out by the body cells. The thirst in these cases of intoxication is an indication that the proteins of the body need more water. "This delicate balance between the cell protein or colloids and the water of the blood will require much more study before we have an intelligent understanding of a few of these important phenomena."

In these conditions of proteose intoxication, they found no evidence of acidosis. This agrees with the findings reported in certain cases of intoxication by Marriott and Howland.

Hurwitz and Whipple* studied the partition of the blood protein fractions and the rise in the serum globulins in experimental intoxications and infections. They found that the serum globulin rose to double its initial value within 48 hours after the production of the obstruction, and the globulins continued high until death. There was a similar rise in serum globulins in animals with chronic intestinal obstruction, and though this increase took place more slowly it often reached a higher level and, as the condition continued, showed a tendency to return to its initial value.

Where peritonitis or an overwhelming intoxication occurred from rupture of the loop, the globulin content of the serum rose with marked

* Hurwitz, S. H., and Whipple, G. H., Jour. Exper. Med., xxv (1917), p. 231.

rapidity, and the blood at times showed a complete inversion to the normal albumin-globulin ratio. They believe that this sudden rise in the blood globulins may be of value in the differential diagnosis of acute conditions associated with the sudden liberation of a toxic exudate.

They conclude that in considering the results of body protein reactions two facts should be kept in mind: (1) That in an acute intoxication there is a marked increase in the globulin fraction at the expense of the albumin portion. During this period there is an increase in the elimination of urinary nitrogen above the normal base line and there is strong evidence that this tissue injury produces a change in the delicate protein balance of the body, and is probably due more directly to a primary cell protein reaction than to the direct action of the poison. (2) In animals receiving small doses of proteose a tolerance is produced during which there is little or no change in the globulin-albumin ratio, which would seem to prove that there was no relationship between the tolerance or immunity developed and the upset in the globulin-albumin fraction. Only in the acute intoxications do you get a marked increase in the globulin even to the point of an inversion of the normal ratio.

Myers* has compiled an interesting table on the significant chemical changes of the blood in disease, most of which is as follows:

In discussing the various figures, as Myers points out, "it is difficult to draw an arbitrary line indicating where normal findings end and pathological begin."

Blood Sugar.—There has been a great deal of discussion about variations of blood sugar under both normal and pathological conditions. The normal values vary from 0.06 to 0.10 or 0.12, and it is generally accepted that the most important factor varying the normal is the food factor. Carbohydrates have a definite effect on circulating blood, where as protein and fat have no effect.

Strouse† studied the normal variations to determine whether water intake and excretion or changes in the weather effect the blood sugar. He concludes that the daily variations depend somewhat on weather conditions, and that increased or diminished water intake and excretion fail to change the blood sugar percentage.

Strouse also studied the normal curve for blood sugar after the ingestion of various amounts of glucose. He thinks that the blood sugar percentage reaction to glucose ingestion may not be an index of disturbed metabolism. In diseased conditions, the blood curve represents a quantitative rather than a qualitative variation from normal. In normal curves, the height of 0.145 is reached in 30 minutes. In severe diabetic conditions, the curve ascends to any height at any time but rarely before an hour, and drops to normal slowly. Apparently the first change toward the abnormal is the delay in reaching the height of the curve. This is shown in the reaction of mild diabetics,

* Myers, V. C., Jour. Lab. and Clin. Med., v (1920), p. 344.

† Strouse, S., Arch. Int. Med., xxvi (1920), p. 774.

in which the curve reached its height in an hour and dropped quickly. Variations from the strictly normal curve suggest a disturbance of sugar mobilization at the time of the test and this disturbance in the curve bears a quantitative relationship to the type of curve presented.

Strouse concludes that "at the present time the reaction (i.e., the sugar curve) cannot be interpreted to mean diabetes or a disturbance of carbohydrate metabolism identical with diabetes, since a similar reaction is found in so many unrelated conditions. Nevertheless, alimentary hyperglycemia has a value in differential diagnosis in obscure cases—a value entirely non-specific and relative to other clinical and laboratory data obtained in the individual case."

Myers* compares the excretion of sugar by the kidneys to a sort of safety valve factor of the body and points out that "the real condition to which attention should be directed is the hyperglycemia and as the disease (diabetes) advances the glycosuria becomes less and less a safe criterion of this, since the permeability of the kidneys for sugar appears to be gradually lowered" as shown by the fact that in advanced diabetes with nephritic symptoms the blood sugar may rise to 0.2 to 0.3 per cent. without showing any sugar in the urine.

From a prognostic as well as a therapeutic standpoint, the study of hydrogen-ion concentration is important as an index of present or approaching acidosis. The blood sugar and the alkali reserve in the body are important as determining factors and as indicating how the disease is progressing.

In nephritis, the study of non-protein nitrogen in the blood becomes important and gives a better indication of kidney function than almost any other of our functional tests, both from the prognostic and therapeutic standpoint. This is perhaps more correct for chronic nephritis than for acute nephritis.

In acute conditions, the elimination of salts is, as we are learning, just as important. The retention of chlorides, resulting from conditions of lowered permeability of the kidneys, and the retention of phosphates in the blood have a great deal to do with the production of acidosis.

Marriott and Howland† have shown that the calcium-phosphate equilibrium in such cases is often very greatly disturbed. Where the phosphates are greatly increased, the calcium content is greatly decreased and acidosis may result.

This balance between calcium and phosphates may be disturbed in such conditions as lead poisoning. In such a case which we have had the opportunity lately to study, the acid phosphates of the blood were found to be increased over 300 per cent. above normal, and this was found without any definite increase either in uremic symptoms or in edema. In such cases there is usually at the same time a tremendous increase in the non-protein nitrogen elements of the blood, so that the

* Myers, V. C., Jour. Lab. and Clin. Med., v and vi (1920); numbers from March, 1920, to October, 1920.

† Marriott, W. McK., and Howland, J., Arch. Int. Med., xviii (1916), p. 708.

Significant Chemical Changes in the Blood in Disease (Myers)

Condition	Urea N, mg. to 100	Sugar, per cent.	Co_2 combining power, c.c. to 100	Creatinin, mg. to 100	Uric acid, mg. to 100	Non-protein N, mg. to 100	Cholesterol, per cent.	Chlorides as NaCL, per cent.	Diastatic activity
Normal	12–15	0.09–0.12	50–75	1–2	2–3	25–30	0.14–0.17	0.57–0.62	15–20
Beginning pathologic	20	0.15	−45	3.5	4	35	0.19	{ −0.55 / +0.65 }	25
Renal diabetes	.....	0.08–0.12							
Mild diabetes	.....	0.15–0.30	.....	.....	....	.....	.....	.....	25–40
Severe diabetes	20	0.30–1.20	50–10	2–4	4–10	.....	0.2–0.8	0.5	35–75
Early interstitial nephritis	15–25	0.12–0.15	.....	2–3.5	5.12				
Acute nephritis	40–100	0.12–0.18	45–20	2–6	5–15				
Parenchymatous nephritis (nephrosis)	20–50	0.12–0.20	.....	2–4	2–5	.....	high	to 0.75	
Terminal interstitial nephritis	60–300	0.12–0.24	40–12	5–28	5–27	100–350	to 0.30	to 0.46	20–50
Double polycystic kidney, to	75	0.20	.....	8	5				
Acute intestinal obstruction	45–120	.....	.....	.....	....	75–170			
Eclampsia	10–25	58–43	.....	.....	....	25–45			
Pernicious anemia	.....	.....	.....	.....	....	.....	to 0.06		

Note.—Taken from "Chemical Changes in the Blood in Disease," by Victor C. Myers, Jour. Lab. and Clin. Med., v (1920), p. 344.

salt balance as well as the non-protein nitrogen balance may be disturbed. In parenchymatous nephritis the retention of salts is greater than that of non-protein nitrogen elements.

In the metabolic disturbances of infancy it is especially important to study the disturbances in the nitrogen retention and in the salt balance. This is intimately associated with the reduction or depletion of water from the system which occurs very rapidly in diarrhea and other intestinal conditions as well as during acute infections, in which the water loss may be from high temperature without necessarily any diarrhea or vomiting. In such cases, acidosis occurs very frequently. As Marriott and Howland and Van Slyke have pointed out, acidosis in these conditions may be corrected without affecting the fatal termination, so that undoubtedly some other factor than the simple acidosis enters into such conditions; and this, as they have pointed out, is very closely related to the rapid changes in internal metabolism caused by rapid loss of water. This is interesting in the light of the experiments of Whipple and his associates to which we have already alluded.

The non-protein nitrogen composition of the blood is receiving of late much more attention than the protein nitrogen, although it constitutes only about 1 per cent. of the total nitrogen of the blood. This is because the non-protein nitrogen factors affect both the anabolic and catabolic processes more than the protein nitrogen, or at least they give us a better insight into what is going on. We are familiar with the fact that in a protein meal there is a temporary elevation in the non-protein and amino-nitrogen of the blood. Myers gives the normal variations for the non-protein nitrogen constituents in mg. to 100 c.c. of blood as follows:

Variations in Non-protein Nitrogen Constituents of Blood (Myers)

	Normal	Early interstitial nephritis	Terminal interstitial nephritis	Parenchymatous nephritis
			to	
Non-protein N	25–30	30–50	350	
Urea N	12–15	12–30	300	30–60
Uric acid	2–3	3.10	25	
Creatinin	1–2	2.4	35	
Creatin	3–7	...	30	
Amino acid N	6–8	...	30	12
Ammonia N	0.1	...	1	

The non-protein nitrogen elements both in health and disease are affected by the state of the internal metabolism and also by the condition of the kidneys. The variations from the normal in the non-protein elements often aid us in the appreciation of what is really happening.

It has been shown by many studies that the various constituents of non-protein nitrogen have different origins. For instance, the urea is largely exogenous, while uric acid is partly endogenous and partly exogenous, under normal conditions of diet and health, and creatinin is almost entirely endogenous. Urea is produced mainly by the liver as a result of the deaminization of amino acids produced during digestion which are not used immediately by the blood. Uric acid, on the other hand, is the result of enzymatic transformation of the amino- and oxy-purins. Creatinin is supposed to be formed in the muscle tissue from creatin.

The distribution of these non-protein nitrogen constituents varies greatly in the blood and urine. The percentage of uric acid in normal blood is greater than in urine, while the urea is much lower; in the case of creatinin and ammonia it is very much lower. It would appear, as Folin and Denis* have pointed out, that the kidney removes creatinin and ammonia with great ease, whereas it is not so easy to remove uric acid. This explains why, in any altered function of the kidney, the blood first shows a retention of uric acid, then urea, and lastly creatinin.

In diseased conditions of the kidneys the normal level of urea and nitrogen in the blood is usually first affected. The relationship between the urea of the blood and the output in the urine should always be carried on together, especially in the study of kidney function. As Addis† has pointed out, the important thing is the ratio between the urea content of the urine and the blood. One may have a high blood urea level with a high urinary output and still have a fairly good functioning kidney, at least one which is able to cope with its situation; whereas if the blood urea is high and the urinary output of urea low, it shows a very much more marked deficiency in kidney function. Urea retention occurs under a great many different conditions besides nephritis.

Lately Addis and Drury,‡ studying blood urea concentration in man, observed that "after the administration of urea and large amounts of water, the ratio shows at first a considerable variability; but after the maximum urea concentration in the blood has been attained, and the concentration is slowly falling, the ratio becomes constant for each individual within fairly narrow limits. Food, excitement and various other factors produce marked variations even under these conditions. . . . Under the special conditions outlined, the ratio varies directly with changes in the blood urea concentration from 118 mg. to 20 mg. per 100 c.c."

Variations in urea retention may occur in cardiac conditions, in syphilis, in anemia and in lead poisoning. In the latter condition we

* Folin, O., and Denis, W., Jour. Biol. Chem., xvii (1913–14), p. 487.

† Addis, T., and Drury, D. R., Proc. of Society for Exper. Biol. and Med., xviii, No. 1 (1920), p. 38, (24 (1606)).

‡ Addis, T., and Drury, D. R., Proc. of Society for Exper. Biol. and Med., xviii, No. 1 (1920), p. 38; (24 (1606)).

have seen the non-protein nitrogen as high as 216 mg. with a urea of 160 mg. per 100 c.c Urea, because of its exogenous origin, undergoes greater fluctuation due to changes in diet; for this reason, it is a very good guide as to the value of treatment, though of less importance from a prognostic standpoint.

Chapin and Myers* conclude from their study in children that "the kidney of the child would appear to act somewhat more efficiently than in the adult, resulting in slightly lower normal figures for the sugar, urea, creatinin and uric acid and a slightly better phenolsulphonephthalein output." Urea retention, because it does not occur as readily in children as in adults, makes the estimation of blood urea an especially helpful prognostic test in the nephritides of children.

Disturbance in the uric acid content of the blood has been reported not only in nephritis but in lead poisoning and leukemia. In advanced nephritis there may be a marked alteration in uric acid retention from the normal of 1 to 3 mg. to as much as 3.5 to 6 mg. per 100 c.c. Lately in a case of lead poisoning, we have noted it as high as 6.4 mg. per 100 c.c. In this case it would be accounted for not only by the increased tissue catabolism but also by the marked involvement of the kidneys. At the time of these findings, the phthalein output was zero. In terminal interstitial nephritis, shortly before death, it may go considerably higher. In leukemia there is undoubtedly an increased formation of uric acid due to the breaking down of leukocytes. In almost all other cases the high uric acid can be accounted for by lack of elimination.

Sedgwick and Kingsbury† show that the uric acid content of the blood of newborn infants is high during the first three or four days. There is also a high output in the urine, and this is in keeping with the fact that uric acid crystals are found so abundantly in the kidneys of the newborn.

Numerous investigators, studying different methods for estimating renal function, conclude that the uric acid concentration of the blood is a most delicate test for estimating kidney function. Where the concentrating power for uric acid is below 14, there are usually clinical symptoms of nephritis; whereas if the concentration is 18 or below, but not as low as 14, there may be no clinical symptoms and yet one is justified in suspecting nephritis. If the concentration for uric acid is 20 or above, the kidneys are probably not involved.

Most physiologists, such as Baumann, Hansmann, Davis and Stevens, feel that creatinin is of endogenous origin and that it is largely produced in the muscles. This opinion is strengthened by the fact that creatinin is the anhydrid of creatin which is the chief non-protein nitrogenous constituent of muscle tissue. Folin, however, was unable to prove that the creatinin in the urine came from creatin when he administered it. About 80 per cent. of creatin

* Chapin, H. D., and Myers, V. C., Amer. Jour. Dis. Child., xviii (1919), p. 555.

† Sedgwick, J. P., and Kingsbury, F. B., Jour. Biol. Chem., xxxi (1917), p. 261.

should appear in the urine, but creatin on administration was entirely lost or disappeared. Folin concludes from this that creatinin and creatin are independent, at least in human metabolic processes.

On the other hand, Myers and Fine have shown that the creatinin content of muscle was greater than that of any other tissue and also that on autolysis of muscle tissue creatin was converted to creatinin at a constant rate of about 2 per cent. daily, which is just about the normal ratio between the muscle creatin and the urinary creatinin.

Under normal conditions creatinin does not vary much in a given individual, the normal being between 1 and 2 mg. per 100 c.c. of blood. There may be slight retention of creatinin in such conditions as syphilis, cardiac conditions, diabetes, and sometimes accompanying high temperatures. This does not usually go as high as 4 mg. per 100 c.c. The reason for its appearance is not definitely known and probably depends on increased tissue breakdown, especially that of muscle. Creatinin retention is usually accompanied by marked urea retention. A retention of creatinin of over 4 mg. per 100 c.c. indicates marked impairment of kidney function.

From a prognostic standpoint the estimation of creatinin is very valuable; less so, however, from a diagnostic or therapeutic standpoint, because when the creatinin is increased in the blood the urea and non-protein nitrogen have also been increased for a considerable period. The increase in the creatinin gives a good indication of the permeability of the kidney. By dietary measures we can affect the output of urea; not so, however, of creatinin. Therefore a kidney that retains creatinin is permanently damaged, and for this reason the estimation of creatinin is the best indicator during the terminal course of the disease.

Sugar is normally present in the blood between 0.09 and 0.12 per cent. This is increased after a meal rich in carbohydrates. The normal sugar curve has a quick rise and a quick descent; it usually does not last more than two hours, the highest peak being obtained at the end of an hour. In diabetes we get the most marked example of hyperglycemia, but a moderate hyperglycemia may also be obtained in certain cases of nephritis and hyperthyroidism.

On the other hand, hypoglycemia is found in cases of myxedema, cretinism, Addison's disease and in diseases of the pituitary glands, and is generally an indication of hypoendocrine function.

In diabetes, particularly in the early stages of the disease, there is a direct relationship between the increased urinary output and the increased amount of sugar found in the blood. In later stages this relationship may not exist, and estimation of the blood sugar is far more important than the amount passed in the urine. There is a definite relationship between the diastatic activity of the blood and conditions associated with the increased amount of sugar in the blood. A high diastatic activity is usually associated with a high blood sugar.

In diabetes mellitus it is especially important to follow the blood sugar curve. In the early stages of diabetes the amount of sugar

passed in the urine may be a real indication of the condition; but in the later stages, as has been shown in numerous studies, there is a certain amount of renal impairment. As the kidney function is involved, the output of sugar in the urine often diminishes, while at the same time it increases in the blood. The estimation of sugar in the blood, therefore, in advanced cases or in rapidly progressing cases of diabetes is far more important as a guide, not only in treatment but also as the best indicator as to how the disease is progressing, and the treatment should attempt to maintain the blood sugar level as nearly normal as possible.

In disturbances of the endocrine glands much work has been done with relation to blood sugar curves.* Unfortunately, a clear interpretation of the blood sugar curve in endocrine disturbances is not always possible. However, we have found it of considerable value in determining the probability of disturbance in the endocrine glands.

A method of making sugar tolerance or carbohydrate tolerance tests is that given by Killian as follows:

"The patient is given, the first thing in the morning, a standard breakfast consisting of two slices of bread, one egg in any form and one cup of water. Two hours after this breakfast the patient empties the bladder and then receives 200 c.c. of water to drink. One hour after this, a specimen of blood and a specimen of urine are taken to serve as controls. The patient then takes glucose, 1.75 gm. per kilogram of body-weight in 50 per cent. solution. Specimens of blood are now taken every hour for three or four hours, the sugar determined and a curve plotted. Following the taking of glucose, a 24-hour specimen of urine is collected and the glucose determined by the Benedict methods, by titration if the amount is large, otherwise by the colorimetric method."†

Since the introduction of simple methods of estimating the carbon dioxide (CO_2) combining power of the blood plasma, much light has been thrown on the phenomena of acid intoxication.‡ Acidosis may result either from the over-production of acid bodies or by their decreased elimination.

The normal slightly alkaline reaction of the blood is maintained by the influence of the bicarbonates, phosphates and proteins of the blood. As L. J. Henderson§ has pointed out, the carbonates may be considered as the first line of defense. During acidosis other acids combine with the carbonates, lowering the body's alkaline reserve.

* Geyelin, Arch. Int. Med., xv (1915), p. 975; Janney and Isaacson, Arch. Int. Med., xxii (1918), p. 160; Bailey, Arch. Int. Med., xxiii (1919), p. 455; Janney, Goodhart and Isaacson, Arch. Int. Med., xxi (1918), p. 188; McCrudden and Sargent, Arch. Int. Med., xxi (1918), p. 252.

† Killian, Proc. Soc. Exper. Biol. and Med., xvii (Feb., 1920).

‡ Van Slyke, Stillman and Cullen, Proc. Soc. Exper. Biol. and Med., xii (1915), p. 165; Van Slyke, Jour. Biol. Chem., xxx (1917), p. 347; Van Slyke and Cullen, Jour. Biol. Chem., xxx (1917), p. 289.

§ Henderson, L. J., Oxford Loose Leaf Med., i (1920), p. 305.

Under normal conditions the kidneys are able to secrete an acid urine from a nearly neutral blood through the medium of acid phosphates, which may be considered as the second line of defense. Marriott and Howland* have shown that it is the acid phosphate line of defense that breaks down in the acidosis of nephritis.

The proteins, both of the blood and of the body cells, are able to take up a considerable amount of acids without any marked change in reaction through their ability to form ammonia.

Myers† gives a number of different criteria as a measure of the degree of acidosis: (1) Lowered carbon dioxide combining power of the blood, (2) lowered alveolar carbon dioxide tension, (3) decreased affinity of hemoglobin for oxygen, (4) reduced alkalinity of the blood (Sellard's test), (5) increased hydrogen-ion concentration of the blood, (6) increased intensity of urinary acidity (hydrogen-ion concentration), (7) the retention of alkali by the body in cases in which the kidney is capable of rapidly excreting an excess of alkali, (8) the simple test suggested by Yandell Henderson of holding the breath; a normal person can hold the breath 30 to 40 seconds without an especially deep respiration, but the period diminishes in proportion to the reduction in the blood alkali.

Van Slyke's method of estimating the carbon dioxide combining power of the blood is probably the method most used and gives very reliable information. The normal carbon dioxide combining power of the blood‡ is from 53 to 77 c.c. of carbon dioxide per 100 c.c. of plasma. For normal infants the figures are about 10 c.c. lower.

Palmer and Van Slyke§ have pointed out a danger in over alkalinizing an individual. This might result in a bicarbonate reduction if the administration is continued after the urine has become alkaline and might indicate a much more severe acidosis than actually exists. They suggest that 0.5 mg. of sodium bicarbonate will raise the plasma carbon dioxide 1 per cent. when the unit of weight is 42 lb. From these figures one could calculate the amount of alkali required to overcome any given acidosis which is due to a reduction in the alkali reserve.

Testing the amount of acetone and diacetic acid in the urine does not give very much indication as to the severity of an acidosis. The estimation of the CO_2 combining power of the blood gives this information much more accurately. This is especially true in following the treatment of diabetes by the Allen method. In severe nephritis the retention of nitrogen and acetone often accompany each other. This type of acidosis is often satisfactorily corrected by the administration of alkali, whereas the acidosis in diabetes is not so easily corrected by the giving of alkali. As pointed out by Allen, fasting will often check the acetone body formation and so affect the acidosis much more

* Marriott, W. McK., and Howland, J., Arch. Int. Med., xviii (1916), p. 708

† Myers, V. C., Jour. Lab. and Clin. Med. (Aug., 1920).

‡ Van Slyke, Stillman and Cullen, Jour. Biol. Chem., xxx (1917), p. 401.

§ Jour. Biol. Chem., xxx (1917), p. 405.

readily than by giving alkali, unless there is coma, when alkali may be the better mode of treating the acidosis.

The acidosis found accompanying severe diarrhea of infants is not due to the presence of acetone bodies, but, according to Howland and Marriott,* is due to the deficient excretion of acid phosphates by the kidneys. In such cases, administration of sodium bicarbonate, as already stated, will often correct the characteristic symptoms and give normal blood tests for alkali reserve; notwithstanding, the child may die. The carbon dioxide in such cases shows an increased acidity which is not affected by giving sodium bicarbonate. In toxic cases, carbon dioxide per 100 c.c. of plasma is estimated by Schloss† to range from 13 to 38 in diarrhea. With ileocolitis, the acetone bodies may be very high, as shown by Moore.‡

Cases Illustrating Acidosis in Children (Chapin and Myers)

Case	Age, months	CO_2 combining power, c.c. to 100	Blood sugar, per cent.	Diagnosis, remarks
1. A. N.....	2	22	0.09	Gastroenteritis; acidosis; death.
2. W. R.....	3½	24	0.10	Gastroenteritis; acidosis; death.
3. Y. W.....	1½	24	....	Gastroenteritis; acidosis; death.
4. M. K.....	10	25	....	Gastroenteritis; acidosis; death.
5. J. T.....	4	26	0.10	Malnutrition; recovery.
6. H. C.....	8½	28	0.09	Malnutrition; acidosis; recovery.
7. J. M.....	12	28	....	Gastroenteritis and rickets; vomiting; improvement.
8. P. K.....	10	33	0.11	Lobar pneumonia; acidosis; death.

Note.—Taken from Chapin, H. D., and Myers, V. C., Amer. Jour. Dis. of Children, xviii (1919), p. 555.

Occasionally following the administration of ether, there is a marked influence on the carbon dioxide combining power of the blood plasma. This may be reduced sufficiently to cause symptoms of acidosis. It has been shown that a preliminary administration of sodium bicarbonate will increase the alkali reserve.§

Henderson‖ has suggested another method of combatting this post-operative acidosis by the administration of carbon dioxide properly diluted with air. This increases the breathing and more rapidly removes the anesthetic from the blood and so restores the pre-operative carbon dioxide combining power.

* Amer. Jour. Dis. Child., xi (1916), p. 309.

† Schloss and Stetson, Amer. Jour. Dis. Child., xiii (1917), p. 218.

‡ Moore, Amer. Jour. Dis. Child., xiii (1916), p. 244.

§ Morriss, W. H., Jour. Amer. Med. Assn., lxviii (1917), p. 1391.

‖ Henderson, Y., Haggard, and Coburn, Jour. Amer. Med. Assn., lxxiv (1920), p. 783.

Cholesterol is found widely distributed throughout the body. Bloor's* work has shown that the average percentage of cholesterol esters in the blood is about 35 per cent. and in the plasma 58 per cent. of the total cholesterol.

Most of the examinations of the blood are made for total cholesterol. An increased amount of cholesterol is found especially in conditions connected with jaundice, obstructive jaundice and also in nephritis and diabetes during acidosis. It is also increased in pregnancy.

Low cholesterol findings are present in anemia. This condition has been studied especially in pernicious anemia in which the concentration of cholesterol may be as low as 0.07, the normal being 0.15 to 0.17.

Rothschild and Wilensky† give the following factors as influencing blood cholesterol:

1. The cholesterol content of the blood is lowered:
   (*a*) By a diet which is poor in lipoids.
   (*b*) By the occurrence of high temperatures.
2. The cholesterol content of the blood is increased:
   (*a*) By a diet excessively rich in lipoids.
   (*b*) By the presence of other diseased conditions, especially diabetes, arteriosclerosis, and nephritis.
   (*c*) During pregnancy. This lasts for a variable period after evacuation of the uterus.
   (*d*) By the presence of obstruction in the common bile duct. If the obstruction, however, is not absolute, as indicated by the degree of accompanying jaundice, the cholesterol content of the blood may not be increased.

Bloor has pointed out that cholesterol is found in higher amounts in the blood of severe diabetes with lipemia; whereas it is not increased in the lipemia caused by over-feeding, this latter lipemia being due to fatty acids alone.

Although cholesterol is increased in conditions connected with jaundice, it is not associated with liver disturbances, nor is it increased in hemolytic icterus.

Luden‡ has suggested that an increased blood cholesterol may weaken the lymphatic defense. As far as we know, there are no studies connected with the cholesterol increase in cases of lymphatic leukemia, though Luden has shown this to be the case in the development of carcinoma. This is a suggestive line for study as a possible etiological factor (i.e., a high cholesterol diet) in the production of leukemia and other conditions connected with a lowered line of defense in the lymphatic system.

* Bloor and Knudson, Jour. Biol. Chem., xxix (1916), p. 7.

† Rothschild and Wilensky, Amer. Jour. Med. Sciences, clvi (1918), pp. 239, 404, 564.

‡ Luden, Jour. Lab. and Clin. Med., iii (1917–18), p. 141; Jour. Lab. and Clin. Med., iv (1918–19), pp. 719, 849.

Certain therapeutic results from the use of cholesterol in pernicious anemia have been pointed out by Pacini* who administered cholesterol in the form of lanolin as an inunction and believed that the condition was somewhat improved.

The connection of blood chlorids with edema is a problem which has been widely studied and the importance of which has been pointed out many times. Edema is usually accompanied by an increased concentration of the chlorids in the plasma. The normal concentration of blood chlorids ranges between 0.45 and 0.47 per cent., and in cases of nephritis with edema this is increased to 0.51 to 0.54 per cent.† In diabetes the plasma chlorides may be increased as high as 0.84 per cent., the normal being 0.57 to 0.62 per cent.‡

The most important reason for making an estimation of the chlorids in nephritis is related to the question of restricting the chlorids in the diet. In many cases there is no need to restrict the chlorids if there is a normal chloride threshold. In other cases salt-free diets are continued too long and the blood reaches a subnormal concentration.

A diminished chlorid retention is found in pneumonia, especially in conditions accompanied by high fever, and in diabetes. In the latter instance this may be due to the fact that there is a large amount of urea and sugar in the blood and that therefore less chlorid is needed to maintain the normal osmotic pressure.

Chlorids are increased in anemia, in certain cardiac conditions, especially those connected with renal involvement, and usually in cases of nephritis with edema.

* Pacini, Amer. Med., xxiv (1918), p. 92.
† Host, Jour. Lab. and Clin. Med., v (1920), p. 713.
‡ McLean, Jour. Exper. Med., xxii (1915), pp. 212, 366.

CHAPTER LXXV

GENERAL TREATMENT OF ANEMIAS

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It has been thought best to group the treatments of anemias and to discuss them in full at this point rather than to repeat them under the various anemias, though the form of treatment most applicable to the different anemias will be mentioned in their appropriate sections.

In the treatment of all anemias there are certain general principles that apply.

Rest.—It is well known that in all anemias the bodily functions are at a lower level than normal, whatever the cause or the type of anemia may be. With rest, bodily functions are carried on at a more efficient level; so that in the simplest types of anemia, rest with appropriate diet may be able to cause a return of the blood functions to normal. This is well illustrated in almost all the convalescent periods following acute infections in which various grades of simple secondary anemia may have occurred. It is often impossible, however, to obtain complete rest during the convalescent period or in cases of mild secondary anemia. Whenever the children suffer from fatigue or when there is evidence of increased cardiac effort, definite periods of rest should be prescribed. We have found that laying down a regimen of so many hours of activity with certain definite periods of rest is often followed by marked improvement in the general condition. This improvement in the general condition of children in secondary anemia usually accompanies definite improvement in the blood picture. Where the anemia is severe and in special diseases of the blood such as leukemia, Banti's disease, etc., the periods of rest should be either continuous or at least much longer than the periods of prescribed activity. In older children it is always well to work out a regimen which will not only give them physical rest but which will keep them in a contented frame of mind. This can be satisfactorily arranged with a little patience by making use of the many forms of entertainment in which children can participate while at the same time keeping fairly quiet; in other words, occupational therapy.

Diet.—Too little attention has been paid to the factor of diet in the regeneration of blood. During the past few years, Whipple and his associates have been studying the factors of diet in relation to blood regeneration in simple anemias produced by hemorrhage. These anemias of course are not necessarily identical with the form of secondary anemias found in children, but their experimental data is

well worth a careful study. They found that following hemorrhages, anemias were very definitely affected by various dietary factors.*

The blood regeneration was closely followed, estimating the increase in hemoglobin, in blood volume and in the pigment volume which is the product of the blood volume times the per cent. of hemoglobin. The pigment volume gives the best general index of the curve of blood regeneration. In their experimental animals, which were young growing dogs, they found the best regeneration was on a mixed diet, the most potent dietary factors being liver, lean beef and spinach (results of spinach experiments from unpublished papers of the same series by Whipple and Robscheit). On simple starvation or a limited bread and milk diet, they found that only a very slow regeneration curve could be obtained. In other words, on a limited diet the maintenance of blood regeneration was alone possible. By maintenance factor is meant keeping the blood—hemoglobin, blood volume and pigment volume—at a level that permits only the replacement due to daily normal blood destruction. On such a diet then it is possible only to replace the daily destruction of red blood cells which amounts in the human to about 3 per cent., taking the life of a given red cell as 30 days. On a more liberal bread and milk diet, the return of the regeneration curve to normal takes from six to eight weeks; on a mixed diet, this same regeneration will take place in from two to four weeks.

They point out very clearly that a diet rich in carbohydrates and practically protein-free except for the milk permits a very slow regeneration curve which takes from four to six weeks and may not then come back to the original normal level. They account for this by the sparing action of carbohydrates which act in two ways: (1) In protecting the body proteins at their source, and (2) in aiding materially in the conservation of protein split-products which are recast into new body protein.

No study of blood regeneration is complete without a study of the bile pigment metabolism and excretion. High carbohydrate diets conserve in the body certain protein factors and so prevent their entering into new formation of hemoglobin which may depend in part upon the type and amount of amino acid groups available from normal protein catabolism. Thus they found that histidine given with sugar appears to cause a production of hemoglobin over the control level, and they suggest that this amino acid may be one of the important elements in the hemoglobin regeneration complex. Casein always had some effect on the hemoglobin regeneration but gliadin had no effect on the regeneration curve. Rice and potato added to bread and milk diet had slight effect on the regeneration curve or on the pigment volume.

Following this experimental work, we have been using at the University of California Hospital in the Children's Department the

* Whipple, G. H., Hooper, C. W., and Robscheit, F. S., Papers I to V, Amer. Jour. of Physiol., liii (1920), pp. 151–282.

following anemia diets which we have found very satisfactory and which apparently definitely affect the regeneration curve of the blood.

ANEMIA DIET NO. I—ONE YEAR

Total for day:

Milk, 24 oz. or ¾ quart
Orange juice, 2 oz. or 5 tablespoons
Spinach, 30 gm. or 2 tablespoons
Liver, 30 gm. or 2 tablespoons
Scraped beef, 30 gm. or 1⅔ tablespoons
Farina, 30 gm. or 2 tablespoons
Zweiback, 3
Broth, 6 oz. or ⅔ cup
Protein, 40; fat, 35; carbohydrate, 77
Total calories, 783

Feedings for day:

6 a.m. Milk, 1 cup
8 a.m. Orange juice, 5 tablespoons with 5 tablespoons water
10 a.m. Milk, 1 cup with 2 tablespoons liver and 1 piece zweiback
2 p.m. Broth, ⅔ cup with 2 tablespoons farina; 1⅔ tablespoons scraped beef and 1 zweiback
6 p.m. Milk, 1 cup with 2 tablespoons spinach; 1 zweiback
10 p.m. Milk, 1 cup

ANEMIA DIET NO. II—18 MONTHS TO 2 YEARS

Total for day:

Milk, 24 oz. or ¾ quart
Orange juice, 2 oz. or 5 tablespoons
Spinach, 50 gm. or 3⅓ tablespoons
Liver, 30 gm. or 2 tablespoons
Scraped beef, 50 gm. or 3 tablespoons
Farina, 30 gm. or 2 tablespoons
Baked potato, 1 tablespoon
Zweiback, 4 pieces
Egg, ½
Sugar, 1½ teaspoons
Apple sauce or prune pulp, 2 tablespoons
Protein, 50; fat, 40; carbohydrate, 127
Total calories, 1068

Feedings for day:

8 a.m. Zweiback, 1; milk, ⅔ cup; farina, 2 tablespoons; sugar, heaping teaspoon
10 a.m. Orange juice, 5 tablespoons with 3 tablespoons water
12 m. Zweiback, 1; milk, ⅔ cup; scraped beef, 3 tablespoons; spinach purée, 3 tablespoons; baked potato, 1 tablespoon
2 p.m. Apple sauce, 2 tablespoons or prune purée, 2 tablespoons; milk, ⅔ cup
6 p.m. Zweiback, 1; milk, ⅔ cup; liver 2 tablespoons; egg, ½; sugar, ½ teaspoon
8 p.m. Milk, ⅔ cup; zwieback, 1

ANEMIA DIET NO. III—2 TO 3 YEARS

Total for day:

Milk, 24 oz. or ¾ quart
Orange juice, 60 c.c. or 4 tablespoons

Zweiback, 5
Scraped beef, 50 gm. or 3 tablespoons
Liver pulp, 50 gm. or 3 tablespoons
Spinach purée, 50 gm. or 3 tablespoons
Egg, ½
Sugar, 1½ teaspoons
Cereal, 50 gm. or 3 tablespoons
Baked potato, 65 gm. or ½ med.
Apple sauce or prune pulp, 2 tablespoons
Protein, 55; fat, 45; carbohydrate, 150
Calories, 1225

Feedings for day:

7.30 a.m. Milk, ⅔ cup; liver pulp, 1½ tablespoons; zweiback, 2; cereal, 3 tablespoons; sugar, 1 teaspoon
12.00 m. Milk, ⅔ cup; spinach purée, 3 tablespoons; zweiback, 1; baked potato, ½ med. with scraped beef, 3 tablespoons; milk, ½ cup; egg, ½; sugar, ½ teaspoon
4.00 p.m. Milk, ⅔ cup; zweiback, 2; apple sauce or prune pulp, 2 tablespoons; liver pulp, 1½ tablespoons
6.30 p.m. Milk, ⅔ cup
10.00 p.m. Orange juice, 3 tablespoons

ANEMIA DIET NO. IV—4 TO 5 YEARS

Total for day:

Milk, 24 oz. or ¾ quart
Orange juice, 50 c.c. or 3 tablespoons or tomato juice, 70 c.c. or ¼ cup
Scraped beef, 55 gm. or 4 tablespoons
Liver pulp, 55 gm. or 4 tablespoons
Spinach purée, 60 gm. or 4 tablespoons
Egg, ½
Sugar, 1 teaspoon (heaping)
Cereal, 60 gm. or 3 heaping tablespoons
Baked potato, 130 gm. or 1 medium sized
Apple sauce, 2 tablespoons or prune pulp, 2 tablespoons
Zweiback, 2 pieces
Butter, 2 small pats
Bread, 2 small slices
Protein, 60; fat, 51; carbohydrate, 177
Calories, 1415

Feedings for day:

7.30 a.m. Milk, ⅔ cup; cereal, 3 heaping tablespoons; scraped beef, 2 tablespoons; Zweiback, 1 slice
12.00 m. Milk, 5 oz. or ⅔ cup; puréed spinach, 4 tablespoons; bread, 1 slice; butter, 1 ball; liver custard (milk, ½ cup, egg, ½, liver, 4 tablespoons); apple sauce, 2 tablespoons or prune pulp
5.00 p.m. Milk, 5 oz. or ⅔ cup; baked potato; scraped beef, 2 tablespoons; zweiback, 1 slice
10.00 a.m. Orange juice, 3 tablespoons
3.00 p.m. 1 slice bread with butter and ⅔ cup milk

ANEMIA DIET NO. V—5 TO 7 YEARS

Total for day:

Milk, 720 c.c. or ¾ quart
Orange juice, 50 c.c. or 3 tablespoons
Scraped beef, 62 gm., 4 tablespoons or 1 medium steak
Liver pulp, 60 gm. or 4 tablespoons

Spinach purée, 70 gm. or 4½ tablespoons
Egg yolks, 2
Sugar, 1 teaspoon
Cereal, 60 gm. or 3 tablespoons
Baked potato, 130 gm.
Apple sauce, 3 tablespoons or 1 baked apple or prunes, 3 tablespoons
Zweiback, 4 pieces
Butter, 2 small pats
Bread, 2 slices
Protein, 72; fat, 60; carbohydrate, 210
Calories, 1670

Feedings for day:

7.30 a.m. Milk, ¾ cup; cereal, 4 tablespoons; sugar, 1 heaping teaspoon; zweiback, 2 pieces; scraped beef, 2 tablespoons
10.00 a.m. Orange juice, 50 c.c. or 3 tablespoons
12.00 m. Milk, ¾ cup; puréed spinach, 4½ tablespoons; toast, 1 slice; 1 butter ball; liver custard (milk, ½ cup, 2 egg yolks, liver pulp, 4 tablespoons); baked apple, 1
3.00 p.m. Milk, ½ cup and Zweiback, 2 pieces
5.00 p.m. Milk, ¾ cup; 1 slice toast; baked potato; scraped beef, 2 tablespoons; 1 butter ball

ANEMIA DIET NO. VI—8 TO 12 YEARS

Total for the day:

Milk, 720 c.c.
Orange, 1
Beef, 1 serving, 90 gm.
Liver, 2 slices, 70 gm.
Spinach, 90 gm. or 4 tablespoons
Egg yolk, 2
Egg, 2
Sugar, 3 teaspoons
Cereal, 3 tablespoons or 60 gm.
Baked potato, 130 gm.
Apple sauce or baked apple, 1 serving
Stewed fruit or prunes, 1 serving
Oil, 2 tablespoons or mayonnaise, 1 tablespoon
Zweiback, 4 pieces
Butter, 4 small balls
Bread, 2 slices
Puréed vegetables in soup
Protein, 83; fat, 120; carbohydrate, 180
Calories, 2144

Feeding for day:

7.30 a.m. Cocoa (1 teaspoon cocoa, ⅔ cup, 1 teaspoon sugar); cereal, 4 tablespoons; milk, ⅓ cup; sugar, 1 teaspoon; zweiback, 1 piece; egg, 1; butter, 1 ball
10.00 a.m. Orange, 1
12.00 m. Cream soup (milk, 1 cup, asparagus and butter ball); toast, 1 slice; butter, 1 ball; beef ball or steak; spinach, 4 tablespoons with hard cooked egg.
3.00 p.m. Boiled custard (½ cup milk, 2 egg yolks and 1 teaspoon sugar); Zweiback, 1 piece
5.00 p.m. Baked potato; 2 pieces zweiback; baked apple; butter, 1 ball; 2 slices liver,; milk, ½ cup
8.00 p.m. 1 cup hot milk; 1 slice toast with butter

As Whipple has pointed out very clearly, where the anemia has been allowed to remain at a low level for any length of time any factor that influences the regeneration curve is put to the hardest test. In their experiments where this low level was produced by keeping the dogs on a simple, low level maintenance diet; i.e., a diet which allowed merely for the replacement of wastage and for no gain over this, they found that a mixed diet with liver, beef and spinach was the best to affect this type of set or chronic anemia. This form of anemia we feel corresponds very closely to the secondary anemias found in infancy and childhood which, from whatever cause they may have been produced primarily, have been kept at a low level due to a minimal diet or a diet containing only milk or milk and carbohydrates. Such cases of secondary anemia respond slowly; but on these special dietaries we have found that they respond better than on any other type of treatment. We have also found the same to be true in anemias of other types and in older children; combined with rest, we believe this to be the method of treatment which will bring the best results.

Fresh Air and Sunlight.—Combined with these two factors of rest and diet, is also the third general line of treatment, i.e., fresh air and sunlight. The value of fresh air, though hard to estimate accurately in physiological terms, is unquestionable from the standpoint of general well being. We have also found that the application of sunlight to these cases is an added benefit.

Sunlight or heliotherapy* if properly carried out, is, we believe, a definite form of stimulation to the blood forming tissues and also an aid to the better functioning of all the body organs. During the past few years much data has been collected on the value of the sun's rays. We have learned of the various rays of the spectrum. Beyond the violet rays we can distinguish certain photographic or ultra-violet rays; and beyond the infra-red rays are the so-called Hertz waves and N-waves, both of which are supposed to be heat waves of various intensity. Beyond the ultra-violet rays at the other end of the spectrum are the *x*-rays or Roentgen rays. From the N-waves, which are the longest waves and the waves with the least frequency per second which have so far been demonstrated, and the *x*-rays, which are the shortest rays and the ones with the greatest frequency per second, we have many variations in wave lengths. All these waves, however, are supposed to have three definite properties—heat, light and chemical action, though these differ quantitatively in the various wave lengths.

Certain definite changes have been demonstrated in the blood due to the sun's rays. There is an increase in the number of red cells and leucocytes and in the percentage of hemoglobin. Arneth's formula is swung to the right by the sun's rays, which means that the older cells have a longer life period. At times there is a definite increase in the eosinophils. There can be no question that the debilitated functions as found in anemia are exhilarated, nutrition is definitely improved,

* Lucas, W. P., Arch. of Pediatrics, xxxvii (April, 1920), p. 193.

activity of secretions is marked, and the internal organs are better oxygenated.

We have drawn up the following regimen for sun treatment which, if carefully carried out in connection with rest and diet, we believe gives the best combination for general treatment of marked secondary anemia.

It is assumed, of course, that in the treatment of any secondary anemia the cause of the anemia must first be removed and that foci of infection, such as tonsils and teeth, must be or have been cared for. It is of primary importance that every source or focus of infection is carefully treated or removed.

Special Forms of Treatment.—It is a time honored custom in anemias to prescribe some form of drug, mainly some preparation of iron or of arsenic. From a clinical standpoint we have assumed that these drugs have a definite and beneficial place in our armamentarium for treating anemias; but, when the literature is analyzed, very little carefully weighed evidence can be found to show that these drugs and not the general regimen have really produced the results which we have been accustomed to attribute to iron or arsenic. It is not to be assumed that we feel that it is time to discard these drugs, but we do wish to throw out the suggestion that in the future more careful evaluations be made, for it would seem possible that our general conception of the value of these drugs will be materially lessened.

This has been very well worked out by Whipple and his associates in a carefully planned series of experiments on the value of certain preparations of iron and arsenic in simple anemias. We have already alluded to their work on simple anemia as influenced by dietary factors in which it was shown that "dietary factors are concerned in the rapid regeneration of hemoglobin; therefore these facts must be considered in evaluating any reaction in conditions of anemia."

We wish now to call attention to some of their work showing the negative influences of familiar drugs upon the curve of hemoglobin regeneration following hemorrhage.* In one series of their experiments on the same type of standard simple anemia in dogs they used Blaud's pills† and found that they were inert as compared with a mixed liver, lean beef or spinach diet.

They also studied the effect of ferric citrate subcutaneously and found that it was inert in comparison with these same dietary factors. It did not compare favorably even with a diet of bread and milk and rice, which, as pointed out, they had found to be better than simply bread and milk.

Ovoferrin was also given by mouth. They did not find that this had any value in blood regeneration but that it simply maintained the "maintenance factor."

* Whipple, G. H., and Robscheit, F. S., VI. Negative Influence of Familiar Drugs upon the Curve of Hemoglobin Regeneration Following Hemorrhage, Arch. Int. Med. (1921).

† Hooper, C. W., Robscheit, F. S., and Whipple, G. H., V. The Influence of Blaud's Pills and Hemoglobin, Amer. Jour. Physiol., liii, p. 263.

REGIME FOR SUN TREATMENT (LUCAS)

Surface to be exposed	Periods of exposure (twice daily)											
	1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day	8th Day	9–12th Days	13–15th Days	16–20th Days	21–30th Days
Feet	3–5	5–10	10–15	15–20	20–25	25–30	35	40	50–60	60	75	90
Legs	...	3–5	5–10	10–15	15–20	20–25	30	35	40–55	60	75	90
Thighs	...	....	3–5	5–10	10–15	20	25	30	30–45	45–60	60	75
Abdomen	...	....	.....	3–5	5–10	15	20	25	30	40	50	60
Forearms	...	....	.....	.....	3–5	5–10	15	20	30	40	50	60
Back	...	....	.....	.....	.....	3–5	5–10	10–15	30	40	50	60
Chest*	...	....	.....	.....	.....	.....	3–5	5–10	15–30	30–40	50	60
Neck	...	....	.....	.....	.....	.....	.....	3–5	10–20	25–35	40–50	60
Trunk	...	....	.....	.....	.....	.....	....	.....	5–20	30–40	50	60
Whole body	3.5	5–10	10–15	15–20	20–25	30	35	40	45	50	55	60

* If there is any cardiac disturbance protect the heart.

Taken from Heliotherapy: Its General Use in Pediatrics, by William Palmer Lucas, M.D., Arch. of Pediatrics, xxxvii (1920), p. 193.

They also used the salt mixture of McCollum amd Simmonds.* This did not have any marked effect on blood regeneration.

"Salt Mixture No. 185 (McCollum amd Simmonds): NaCL—8.65 gr.; $MgSO_4$ (anhydrous)—13.30 gr.; NaH_2 PO_4H_2O—17.35 gr.; K_2HPO_4—47.70 gr.; CaH_4 (PO_4) $_2H_2O$—27.00 gr.; Fe citrate—5.9 gr.; Ca lactate—65.0 gr. Iron equivalent to 64 mgr. or 0.96 gr. daily."

They tried the effect of arsenic in the form of Fowler's solution by mouth and sodium cacodylate subcutaneously. With Fowler's solution, the curve of hemoglobin regeneration showed a very slow rise from week to week and only approached normal after five or six weeks. This did not differ in effect when the animals were transferred to a larger food intake (ampler amounts of milk and bread without a mixed diet of meat or liver or spinach). They point out that when a dog gains in weight rapidly the curve of regeneration may not show itself by ordinary tests, but if blood volumes are taken it can be shown that the curve is a definite upward one rather than a stationary one. We have had an opportunity of testing this out in following the blood volumes of several infants with secondary anemia, the secondary anemia being due to dietary factors.

The curve of blood regeneration when using sodium cacodylate subcutaneously rose slowly and uniformly during 11 weeks but never returned to normal. This reaction is typical of many recorded for bread and milk alone. After such a period, a change to a mixed diet gives a prompt increase in all hemoglobin figures and the normal level is reached in three weeks.

They say that "no drug has been tested which can compare with the meat factors in stimulating a rapid regeneration of hemoglobin during these anemia periods induced by simple hemorrhage. These carefully controlled experiments give no support to the time honored custom of administering iron and certain other drugs in conditions of simple anemia." They believe "it will be of much clinical importance

Iron may be administered in the form of:

	Dose			
	6 mo.	18 mo.	3 yr.	5 yr.
Syrup of the iodid of iron (5 per cent. ferrous iodid).....	3 drops	6 drops	10 drops	20–30 drops
Blaud's pills, 1–5 gr.				
Citrate of iron, 1–3 gr. given hypodermically.				
Cacodylate of iron (S. C.) (3 per cent. solution) given hypodermically.	½ c.c. (iron cac.0.015)	1 c.c. (iron cac.0.03)	2 c.c. (iron cac.0.06)	4 c.c. (iron cac.0.12)

* McCollum and Simmonds, Jour. Biol. Chem., xxxiii (1918), p. 63.

Arsenic may be administered in the form of:

Given in the form of Fowler's solution. It is best given in water. It is usually given in increasing doses, beginning with the minimum and working up to the maximum.	½ drop (arsenic 0.00033)	1 drop (arsenic 0.00066)	2 drops (arsenic 0.0013)	2–5 drops (arsenic 0.0013–0.0033)
Cacodylate of soda (S. C.) (5 per cent. solution) given hypodermically.	½ c.c. (arsenic 0.025)	1 c.c. (arsenic 0.05)	2 c.c. (arsenic 0.10)	4 c.c. (arsenic 0.20)

to record accurate observations in human cases, giving particular attention to a variety of diet factors." They also suggest that in chlorosis it would be interesting to collect accurate data on the influence of diet factors alone.

Benzol Treatment.—Since Selling's* observation that benzol has a definite effect on reducing the number of leukocytes, the use of benzol in the treatment of the leukemias particularly has gained a great deal of attention and favor.

Billings† has remarked that benzol may be very beneficial but also that it may be very disastrous. When benzol is used, great care should be taken in following the leukocyte count, and it should be immediately discontinued when the count falls to 25,000 or 20,000. The fall may often be very rapid and continue for some days after benzol has been discontinued. This cumulative action offers the most dangerous possibilities and should be guarded against, for numerous fatalities have been reported in which the leukocyte count continued to fall even below 1000 after benzol had been discontinued. In appropriate doses the red cells may be stimulated and increased somewhat in number, at times amounting to polycythemia. It should never be administered in the acute cases. It is only applicable to the more subacute and chronic cases which on the whole in infants and children are numerically fewer than the acute cases; so that its administration in infants and children should never be carried on unless the child is under absolute and careful observation where the blood count can be done daily.

It is administered in capsules containing from 0.1 to 0.3 gm. benzol mixed with equal parts of olive oil which diminishes the irritating effect. The capsules should be coated with salol. The dosage can be slowly increased until from three to five capsules are given daily. It should be given immediately after meals.

If there are any gastro-intestinal disturbances or other symptoms, such as headache, dizziness or increase in hemorrhages, benzol treat-

* Selling, L., Johns Hopkins Hosp. Bull., xxi (1910), p. 33.
† Billings, F., Jour. A. M. A., lx (1913), p. 495.

ment should be discontinued notwithstanding the blood picture, for serious consequences have followed these symptoms. The results from benzol are at best only temporary and on the whole are not to be compared with the effects of *x*-ray or radium treatment.

X-ray and Radium Treatment.—During the past decade *x*-ray and radium treatments have received wide attention. They are at present undoubtedly the best therapeutic agents we have in the treatment of conditions in which there is splenomegaly and especially so for the leukemias. In some cases of splenomegaly, such as Banti's disease, splenectomy may be the better treatment. There are few conditions in which more gratifying temporary results are obtained than with the *x*-ray or radium treatment of chronic leukemia. In these cases the reduction of the size of the spleen and the general betterment of the patient are often very striking, amounting almost to a complete state of well being, though in no cases so far reported have there been any permanent cures. The results in chronic leukemia will last for months and years, especially if cases are kept under observation and treatments repeated at appropriate intervals, depending upon the general condition and the blood picture of the patient.

There are, however, certain dangers in the application of *x*-ray treatments which have been carefully considered in the experimental work of Hall and Whipple.* These investigators have studied the effect of toxic and lethal doses of the *x*-ray on dogs. They show that there is a definite increase in the nitrogen output in the urine and also a marked increase in the non-protein nitrogen of the blood which may rise to more than 100 per cent. of the normal. The toxic symptoms reach their climax on the fourth day.

They find that the anatomical changes produced by the constitutional *x*-ray intoxication are as follows:

The spleen is decreased in size, becomes fibrous and contains fewer lymphocytes than normal. The bone marrow shows a decrease in cells. The gastro-intestinal tract shows the greatest change. The contents may be slightly blood-tinged or even quite dark in the colon, but there are no ulcers. There is a marked increase in the autolysis of the intestinal epithelium. Often the intestinal epithelium was found completely autolyzed, leaving only a few epithelial fragments.

The results of this injury compare closely with certain "non-specific" reactions which they have found in the study of intestinal obstruction which are due to the great breakdown of tissue proteins as indicated by the nitrogen elimination in the urine and the accumulation of non-protein nitrogen in the blood.† This intoxication may be somewhat diminished by the intravenous injection of glucose solutions, and they suggest that the intravenous administration of glucose may be the proper treatment for severe cases of general intoxication from *x*-rays.

* Hall, C. C., and Whipple, G. H., Amer. Jour. Med. Sciences, clvii (1919), p. 453.

† Whipple, Cooke and Stearns, Jour. Exp. Med., xxv (1917), p. 479.

Their general conclusions* are given in full because of their special relation to the present wide use of the *x*-ray in treatment of blood conditions.

"The general constitutional reaction of dogs given a lethal dose of hard Roentgen rays from the Coolidge tube is remarkably uniform and constant. A double lethal dose will not modify the clinical reaction. A latent period of 24 hours or longer is the rule and during this time the dog is normal except for an increased urinary nitrogen. Vomiting and diarrhea then dominate the clinical picture until death, which as a rule follows on the fourth day.

"The blood non-protein nitrogen commonly shows a marked increase (twice normal) on the day before death and often more than three times normal on the day of death.

"The elimination of urinary nitrogen is increased on the day following the Roentgen-ray exposure and remains high until death, often an increase of 50 to 100 per cent. above the normal base line.

"Autopsy findings are: A spleen which is small and fibrous, a moderate grade of congestion and mottling of the intestinal mucous membrane and strong evidence for epithelial injury in the intestinal mucosa. The epithelium lining the intestinal crypts may show actual necrosis and invasion of polymorphonuclear leukocytes. This epithelium also shows a remarkable speed of autolysis and may vanish by autodigestion within a few hours post-mortem.

"The epithelium of the small intestine apparently is sensitive to large doses of the Roentgen rays, and the injury of these important cells may furnish the correct explanation of the general intoxication associated with the vomiting and diarrhea.

"The so-called Roentgen-ray anaphylaxis or hypersensitiveness to a second properly timed Roentgen-ray exposure finds no support in our experiments. In fact, there is some evidence for a slightly increased tolerance to the second dose.

"Chloroform injury and the associated liver necrosis do not modify the reaction of the dog to large or small doses of the Roentgen rays. This is evidence that the liver epithelium is not fundamentally involved in the fatal Roentgen-ray intoxication.

"Our experiments yield no evidence of Roentgen-ray nephritis.

"Increasing the width of the spark gap increases the hardness or penetration of the Roentgen rays, and this greatly increases the severity of the constitutional reaction and subsequent intoxication.

"Burns caused by the Roentgen rays are not associated with any distinct increase in urinary nitrogen during the long latent period between the Roentgen-ray exposure and the early dermatitis which precedes the actual ulcer. We know of no satisfactory explanation for this long latent period, which may last for three weeks.

"This Roentgen-ray intoxication or general constitutional reaction is a good example of a 'non-specific' intoxication. Much important

* Hall and Whipple, Amer. Jour. Med. Sciences, clvii (1919), p. 453.

information can be obtained by further study of this condition and will well repay the effort."

The same general results have been commented upon in human cases by Giffin,* Peabody,† and by Ordway, Tait and Knudson.‡ They have shown that there is a marked increase in urinary nitrogen excretion and also in the retention of non-protein elements in the blood following both *x*-ray and radium treatment. It is important, therefore that before and after both *x*-ray and radium treatments a careful observation on these factors should be carried out as well as on the blood picture. If this is done we are sure that fewer unfavorable results will follow the application of either *x*-ray or radium treatment.

As pointed out by Hall and Whipple, it is important to regulate the spark gap, for they found that there was considerable difference in the penetrability and hardness of the rays, depending on the length of the spark gap. The fatal dose, for instance, for a dog is about 500 ma. minutes with a 6-in. spark gap, whereas the fatal dose is only 210 ma. minutes with a 9-in. spark gap. They feel, that this fact is not clearly recognized even by roentgenologists and believe that it should be emphasized.

In the application of radium it is important that the radium should not be applied to the same area too often. Intervals of at least four to six weeks should intervene before the same area is used. For this reason cross radiation has been introduced. It is well to outline carefully the area of the enlarged spleen and to apply a thin cotton binder which takes in the upper costal margin above and the bony pelvis below. On this binder the spleen is carefully outlined and various areas marked off and numbered. A chart of this can be kept, so that on the repeated application of radium the same area will not be used in the same series of treatments. In this way, the spleen can be attacked from the front, back and from the left side. A careful chart should be kept of the areas exposed.

It is important also to protect the radium laterally as well as anteriorly. For this purpose Giffin§ recommends the blocks devised by Tucker, "1.25 cm. of wood, 2 mm. of lead, 1.25 cm. of wood bored to receive the tubes of radium and above this 2 mm. of lead and another 1.25 cm. of wood." This is held in place by a canvas belt.

From 100 to 50 mg. of radium element or millicuries of radium emanation are employed. This may be used from four to six hours respectively, depending on the amount of radium. The series is repeated after an interval of from four to six weeks, depending on the general condition of the patient estimated by the blood picture, size of the spleen, and whether the non-protein nitrogen retention in the blood has returned to normal, and the urinary nitrogen output decreased to within normal limits.

* Giffin, H. Z., Med. Rec., cxiv (1918), p. 1020.

† Peabody, F. W., Boston Med. and Surg. Jour., clxxvii (1917), p. 873.

‡ Albany Med. Annals, lxi (1920); Trans. Assoc. Amer. Physicians, xxxi (1916), p. 177.

§ Giffin, H. Z., Amer. Jour. Roentgenol., v (1918), p. 292.

With these guides it should be possible to treat successfully the more subacute or chronic cases; and its application in such conditions as Banti's disease, Gaucher's disease and other conditions with splenomegaly where splenectomy is not thought advisable offers at least considerable hope of giving relief. In certain of these latter conditions, *x*-ray or radium treatment may so improve the condition that splenectomy may be thought advisable after one or two series of *x*-ray or radium treatments. Giffin has reported such a series of cases at the Mayo Clinic.

Splenectomy.—Splenectomy is a surgical procedure but it will be mentioned here, for the advisability of performing splenectomy often comes up in cases of splenomegaly. In early Banti's disease there is no procedure which equals the value of splenectomy. If performed in the first stages, we can hope for a practical cure; in the later stages it may be advisable to perform splenectomy to relieve the discomfort from the enlarged spleen but without much hope of its checking the primary condition. It may lengthen life though it holds great surgical risks. It is a doubtful procedure in the splenomegaly found in leukemia, pernicious anemia or aplastic anemia. In Gaucher's disease it may have some effect in prolonging life, though it probably does not offer the same hope of cure as in Banti's disease.

Transfusion.—The indirect method of blood transfusion has become a medical procedure of great value during the last decade. In hemorrhages of the newborn it is the treatment of choice and is life-saving in most instances except those which are due to acute sepsis. In other hemorrhagic diseases, such as purpura hemorrhagica, and during the hemorrhagic periods of leukemia, pernicious anemia, aplastic anemia and hemophilia, it is often a stop-gap procedure which is of great value in checking hemorrhage and prolonging life, though at times in some of these conditions its value is short lived. In cases of traumatic hemorrhage or in chronic hemorrhage it is of great value after the primary hemorrhage has been stopped, especially if the loss of blood has been considerable. In acute traumatic hemorrhage, if the loss of blood is less than 50 per cent. of the estimated total blood volume of the child, the liberal administration of fluid will probably bring back the blood volume to normal very rapidly; but when the blood volume has been reduced so that the hemoglobin content is as low as 20 or 25 per cent., there is no procedure which will give as brilliant and immediate relief as does the introduction of a moderate (not excessive) amount of blood intravenously.

This has been well shown by the work of Robertson and Bock* who found that "the organism did not restore its blood volume beyond a certain point when a further increase in it would, by dilution, have brought the hemoglobin per cent. to a very low figure. In such cases a further increase of the blood volume occurred only when the hemoglobin rose. . . . With a total hemoglobin reduced to 25 per cent.

* Robertson, O. H., and Bock, A. V., Jour. Exper. Med., xxix (1919), pp. 139 and 155.

or under, transfusion is needful. New blood is necessary, not only to supply more oxygen-carrying cells, but also because it actually enables the circulation to increase its volume." It is necessary for the hemoglobin percentage to be above this point if the blood volume is to be restored by the organism's own activities. They point out the value of blood volume estimations and also the importance of estimating the percentage of reticulated red cells as a sign of blood regeneration.

The factors underlying blood coagulation and some of the known factors regarding blood regeneration have already been discussed.

Group Tests for Transfusion.*—Blood transfusion was discussed by the Faculty of Medicine of Paris as early as 1668, and at that time an edict was put forth forbidding transfusion except when sanctioned by the faculty. In 1818, Blundell reported on some experimental work in transfusion from one animal to another and commented on the results achieved by this method after severe hemorrhage. In 1874, Hasse described certain unfavorable symptoms which arise following the injection of blood from different or antagonistic species. The symptoms described were rigors, fever, suppression of urine or hematuria. It had already been shown by Landois that the serum of some animals possesses the property of dissolving that of other animals.

These unfavorable results vary considerably. They may be very slight or they may be so severe that death quickly follows. In some cases, reaction may be noted as late as 12 to 18 hours after transfusion. The experimental work on isohemagglutinins and isohemolysins explains a great many of these unfavorable results but not all. These two bodies are not entirely interdependent though they are ordinarily considered as such. Isohemagglutinins were first discovered by Landsteiner and by Shattuck independently of each other.

Every human being, it has been found, belongs to one of four blood groups. This grouping is based on the agglutinating activity of human serum and the susceptibility of red blood corpuscles for agglutination. Jansky first described these four groups in 1907. Jansky's classification is as follows:

TABLE I.—JANSKY CLASSIFICATION

Cells	Serum			
	I	II	III	IV
I	−	−	−	−
II	+	−	+	−
III	+	+	−	−
IV	+	+	+	−

NOTE.—Jansky, J., Hämatologische Studien bei Psychotikern. Sborn. klin., v. Praze, viii (1906–7), p. 85. Ref. Jahresb. f. Neurol. u. Psychiat. (1907).

* Karsner, H. T., Jour. A. M. A., lxxvi (1921), p. 88.

Table II.—Reaction of Serum and Corpuscles (Jansky)

Group I	Serum agglutinates cells of Groups II, III and IV.
	Cells agglutinated by no serums.
Group II	Serum agglutinates cells of Groups III and IV.
	Cells agglutinated by serums of Groups I and III.
Group III	Serum agglutinates cells of Groups II and IV.
	Cells agglutinated by serums of Groups I and II.
Group IV	Serum agglutinates no cells.
	Cells agglutinated by serums of Groups I, II and III.

In 1910, Moss offered a similar grouping, in which Group I appears as Group IV according to Jansky's classification; in other words, he transposes the order. This has led to a great deal of confusion.

Table III.—Moss Classification

Cells	Serum			
	I	II	III	IV
I	−	+	+	+
II	−	−	+	+
III	−	+	−	+
IV	−	−	−	−

The Moss classification* may be stated as follows:

Group I. Serum agglutinates no corpuscles. Corpuscles agglutinated by the serum of Groups II, III, and IV.

Group II. Serum agglutinates corpuscles of Groups I and III. Corpuscles agglutinated by the serum of Groups III and IV.

Group III. Serum agglutinates corpuscles of Groups I and II. Corpuscles agglutinated by serum of Groups II and IV.

Group IV. Serum agglutinates corpuscles of Groups I, II and III. Corpuscles agglutinated by no serum.

Numerous studies have been carried out as to the incidence of these four groups.

Happ† has studied the development of isohemagglutinins from birth up to 10½ years of age. He finds that the red blood cells first take on the special group characteristics, but these group characteristics of the cells may be changed when the serum takes on the definite group characteristics. After the serum has definitely taken on a grouping there is no further change. The permanency of the grouping takes place usually sometime between the first and second year. Fixed grouping was found from birth to the first month in 16.3 per cent.; from 1 to 3 months, 22.2 per cent.; from 3 to 6 months, 31.8 per cent.; from 6 to 12 months, 69.5 per cent.; from 1 year to 10½ years, 96.8 per cent.‡

* Moss, W. L., Johns Hopkins Hosp. Bull., xxii (1911), p. 238.
† Happ, W. M., Jour. Exper. Med., xxxi (1920), p. 313.
‡ Happ, W. M., Jour. Exper. Med., xxxi (1920), p. 325, Table VI.

We can confirm this work of Happ's by a similar investigation which has been carried on by Gelston* at the University of California Hospital, who has also found that the isohemagglutinins are first established in the cells and then in the serum and that there may be a shift in the cells from one group to another. Breast milk has been found to have agglutinins which correspond with those of the mother's own blood, but they are not transmitted through breast milk. Both bottle fed babies and breast fed babies apparently develop their isoagglutinins independently of their mother. The isohemagglutinins and isohemolysins follow the Mendelian law. The incidence of the four groups in children, after the grouping has become established, is practically the same as in adults.

TABLE IV.—INCIDENCE OF THE FOUR GROUPS IN MAN

	Jansky, per cent.	Moss, per cent.
Group I	42.84–45	5.42
Group II	10.36	40.0 –41.38
Group III	40.0 –41.38	10.36
Group IV	5.42	42.84–45

The interagglutinability of the blood has not been entirely explained. The exponents of Ehrlich's side-chain theory believe that human blood contains two agglutinins, *A* and *B*, and also two receptors, *a* and *b*, for these agglutinins. According to this theory, a serum which does not agglutinate the corpuscles of any blood contains neither agglutinin *A* nor agglutinin *B*; and a serum which agglutinates all corpuscles contains agglutinins *A* and *B*. Conversely, the corpuscles that contain both receptors *a* and *b* are agglutinated by all serums of the other groups; and corpuscles that do not contain the receptors *a* or *b* are not agglutinated by any serums.

The distribution of these agglutinins and receptors is shown in the following table:

TABLE V.—DISTRIBUTION OF AGGLUTININS AND RECEPTORS (KARSNER)

Jansky	Agglutinin (serum)		Receptors (cells)	
Group I	*A*	*B*	—	—
Group II	*A*	—	—	*b*
Group III	—	*B*	*a*	—
Group IV	—	—	*a*	*b*

NOTE.—Karsner, H. T., Jour. A. M. A., lxxvi (1921), p. 91, Table V.

This problem, however, is not settled, as pointed out by Karsner, and there may be some physico-chemical laws that govern this inter-

* Gelston, C. F., Am. J. Dis. Child., XXII (1921) p. 351.

agglutinability. Karsner has shown that if serum is desiccated the agglutinins deteriorate and acquire the power of "non-specific agglutination so that each of the serums can agglutinate the cells of all the groups." The buffer value of the serum changes. There is an increase in the hydrogen-ion concentration of the serum, and it may be that certain colloidal reactions and physico-chemical laws offer a different explanation for this interagglutinability.

It has been shown that it is safe to transfuse a blood whose serum agglutinates the patient's red blood cells, but it is dangerous to inject a blood whose red blood cells are agglutinated by the patient's serum. For this reason, individuals of Group I (Jansky) or Group IV (Moss) are considered as "universal donors."

This is a safe rule to follow in most cases; but where the red blood cells and the blood volume are markedly diminished it is always wise to test out the donor's cells against the patient's serum, for in these pathological conditions certain abnormal reactions at times occur. These reactions may take place in pathological conditions even when the donor belongs to the same group, but they are usually not very severe if the transfusion is done with careful technique. On the whole, it is preferable in these markedly pathological conditions with low blood volume and reduced red blood cells to use a donor from the same group as that of the patient. It is perhaps wiser not to introduce too large a quantity of blood; it is better to repeat the transfusion oftener than to rely on one large transfusion.

Notwithstanding all precautions, there are a certain number of disagreeable results that at times follow transfusion which are probably due to the production of some toxic material such as anaphylatoxin. In certain anemias the agglutinin titer is so low that it does not cause agglutination when mixed with the donor's cells. For this reason it is also usually best to have standard serums with high agglutinin titer for testing. It is well to establish the definite group to which the patient's blood belongs as well as that of the donor. This can easily be done by having on hand serum from Group II and Group III and testing against these the red blood cells of the patient to be transfused. The group to which the patient belongs may be determined from the following table:

CORPUSCLE TEST AGAINST KNOWN SERUM

Corpuscles	Serum		Group to which x belongs. (Moss' grouping)
	Group II	Group III	
x	+	+	I
x	0	+	II
x	+	0	III
x	0	0	IV

x = agglutination. 0 = no agglutination.

The apparatus and method for testing blood groups are as follows:

Apparatus and Material Required.—The technique employed requires:

1. Hollow-ground slides.
2. Cover-slips.
3. Test tubes.
4. Physiologic salt solution (0.85 per cent.).
5. Platinum or nicrome wire loop.
6. Bunsen burner.
7. Microscope.
8. Group II and Group III serum.

Collection and Preservation of Known Sera. (*a*) *In Capillary Pipettes.*—The collection and preservation of Group II and Group III serum are accomplished thus: Five c.c. of blood are withdrawn from an arm vein of a Group II individual, and the same amount from a Group III individual, placed in a sterile centrifuge tube, allowed to clot, centrifugalized and the serum transferred to other sterile tubes. From the latter, capillary pipettes are to be filled.

A number of capillary pipettes are prepared from glass tubing 3 or 4 mm. in diameter by drawing each end out into a capillary. The capillary at one end is cut off within 1 in. of the body of the tube. That at the other end is left 6 or 8 in. long. These are sterilized and half are used for the Group II and half for the Group III serum, the long capillary stems being filled half full of serum, the tubes tilted so that the end of the column of serum will be about an inch from the end of the capillary, and then both ends of the tube sealed in the flame. Two file marks on the glass indicate the tubes containing Group III serum. The tubes are stored away in boxes in the refrigerator or at room temperature but protected from the light. These tubes may be kept in the laboratory and are ready for immediate use whenever required. Serum preserved in this way retains its agglutinating power six months or longer.

(*b*) *Serum Dried on Cover-slips.*—Cover-slips are cleaned and dried. On some of these are placed two loopfuls of serum from persons of Group II. In a like manner cover-slips are prepared with serum from Group III persons. These droplets of serum are allowed to dry in the air, and are wrapped in paper and placed in the ice-box. Such dried sera maintain their agglutinating properties for two months and longer.

Methods.—A single drop of blood from the finger tip or ear is allowed to fall into a test tube containing 8 or 10 c.c. of physiological salt solution (0.85 per cent.). The tube is rotated or shaken in order to obtain a uniform suspension. On each of two cover-slips a very small drop of the corpuscle suspension is placed by means of a capillary pipette or platinum loop. To one a drop of Group II serum is added, and to the other a drop of Group III serum. The serum and corpuscles are mixed on a cover-slip, inverted over a hollow-ground slide, and examined under the microscope. Agglutination may take place in

a few minutes at room temperature, but it is safer to allow half an hour at 37°C. to elapse before concluding there is no agglutination.

Alternative Technique.—If the known Group II and Group III sera are available in dried form, it is simply necessary to add one loopful of corpuscle suspension from the patient to be tested to each of two cover-slips containing dried Group II and Group III sera. The dried serum is thus dissolved. The cover-slips are now inverted over a hollow-ground slide and studied microscopically for agglutination.

Safe Transfusions.—It is preferable but not always necessary in transfusion that donor and recipient belong to the same group. The essential for safety is that the serum of the recipient should not agglutinate the corpuscles of the donor. The diagram tells at a glance to what group a person must belong in order to be a suitable donor for an individual of another group. If the arrow points toward the patient's group, and away from the group of the donor, the transfusion may be done with safety. It must always be remembered that on the diagonal connecting Groups II and III the arrow points in both directions, and that blood in these reciprocal groups should never be interchanged. It is evident then that 100 per cent. of persons may be used as donors for patients of Group I, 83 per cent. for those of Group II, and 50 per cent. for those of Group III. For those of Group IV, only 43 per cent. are available as donors, as a patient of this group must have a donor of this group. Group I (Moss) is a universal recipient; Group IV (Moss) is a universal donor.

The following is a diagram showing the interrelation of the iso-agglutination groups.*

As has been stated, the indirect method of transfusion has been universally adopted. There are two main methods employed at the present time, one in which a paraffin-coated needle and glass cannula and syringe are used. Lindemann† has described such a syringe, but it requires considerable technique in the handling. On the whole, unless one is well experienced with its use, we would advise instead the use of citrated solutions which was the method for blood transfusion adopted in the A. E. F. during the past war and has been in general use both before and since that time.

Drinker and Brittingham‡ have studied the reactions following transfusion of citrated blood. They conclude that there may be a rise in temperature of 2.5°F. following a citrate transfusion but that there is no constant relation of the reaction to the method of citration or the specimens of citrates. They found that citrated plasma which has been freed from cellular elements was non-toxic in compatible individuals, whereas the washed cells were always toxic. Their final conclusion is as follows:

* Sanford, A. H., Jour. A. M. A., lxx (1918), p. 1221.

† Lindemann, E., Amer. Jour. Dis. Children, vi (1913), p. 28; and Jour. A. M. A., lxxii (1919), p. 1661.

‡ Drinker, C. K., and Brittingham, H. H., Arch. Int. Med., xxiii (1919), p. 133.

"While the totals of the different types of transfusions which have been employed are not large, it appears that three elements make up the final total of reactions in citrate transfusions: (*a*) Very rare gross incompatibilities which escape *in vitro* detection; (*b*) changes in the plates, part of the process of coagulation; (*c*) direct action of the sodium citrate on red cells promoting hemolysis."

The citrate method is by all means the simplest and can be done by one person with the aid of a nurse. The blood to be transfused should be collected into a sodium citrate solution so that the final strength after the blood is diluted will be over 0.25 per cent. of citrate. This will inhibit coagulation. Citrate solution is made up in 10 per cent. solution, stoppered with gauze and autoclaved for 15 minutes

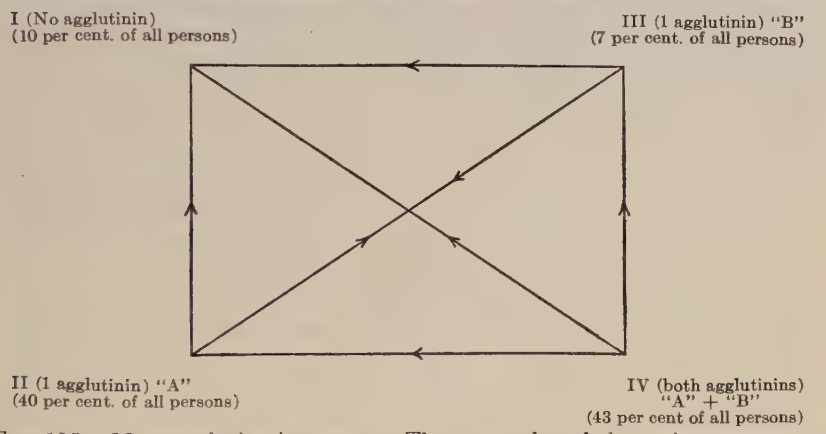
I (No agglutinin)
(10 per cent. of all persons)
III (1 agglutinin) "B"
(7 per cent. of all persons)
II (1 agglutinin) "A"
(40 per cent. of all persons)
IV (both agglutinins)
"A" + "B"
(43 per cent of all persons)

FIG. 135.—Moss agglutination groups: The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead.

under 15 pounds of pressure. If 500 c.c of blood are to be transfused, 15 c.c. of this 10 per cent. sodium citrate solution are put into a sterile liter flask and blood is drawn directly into the flask from the donor's vein through a rubber tubing connected up with a glass tube which enters the flask through a rubber stopper. Of course, everything used must be carefully sterilized and rinsed out well with citrate solution. If a second glass tube is connected up through this rubber stopper, suction can be produced to accelerate the flow of blood. The exact amount of blood to be withdrawn should be originally marked on the flask; i.e., if 300 or 500 c.c. of blood are wanted, this should be marked on the receiving flask before starting. By gently rotating the flask while the blood is flowing in, a thorough mixture of the citrate with the blood takes place immediately and no clotting will occur. If clotting should occur, the blood must be carefully filtered through a sterile towel. This may be a wise procedure in all cases, as it is often difficult to tell whether fine fibrin clots have formed or not. Otherwise the same flask can be used as an injecting flask by simply changing the stopper and connecting it up with glass tubing in the flask and rubber

tubing connecting this with the injecting needle, all of which have been washed in citrate solution, after having been sterilized. In this way blood can be introduced directly into the longitudinal sinus by using the Goldbloom needle.* An ordinary injection needle can be used for the jugular vein in the neck or one of the arm veins at the elbow. At times the volume of blood is so much reduced that the vein must be cut down on, though this does not happen often when one is accustomed to entering children's veins.

Blood transfusions are indicated whenever there has been any great loss of blood, as has already been pointed out and clearly demonstrated by the work of Robertson and Bock. In marked secondary anemias where the blood volume and hemoglobin are very low, i.e., between 25 and 50 per cent., the blood condition will be assisted in returning to the normal level by the aid of a moderately small transfusion of blood, providing the primary cause has been relieved. Large transfusions are not indicated in such conditions. In hemophilia, as will be pointed out, and in purpura hemorrhagica, transfusions are often of great value in checking hemorrhage, though they in no way cure the condition. On the other hand, in many of the hemorrhages of the newborn, transfusion is life-saving. If done early, a comparatively small amount of blood transfused will stop the hemorrhages and cause a rapid return to normal. Where the bleeding in the newborn is due to sepsis, however, relief does not occur as readily.

In aplastic anemia and in the leukemias, transfusions are often considered, but they hold out only scant hope for continuing life a short time. They may or may not have any definite effect on stopping the hemorrhages. We have seen cases of leukemia and aplastic anemia bleed almost as much following a transfusion as they did before transfusion was performed. In the diminished blood volume associated with athrepsia and malnutrition, we have not had any success in stimulating or assisting recovery by transfusions. The pathological and physiological derangements in these conditions are of such a nature that they apparently do not respond to the stimulation given by transfusion.

* Goldbloom, A., Amer. Jour. Dis. Children, xix (1920), p. 229; Amer. Jour. Dis. Children, xvi (1918), p. 359.

CHAPTER LXXVI

CLINICAL DISCUSSION OF SIMPLE AND SECONDARY ANEMIA

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Anemia may be defined as a condition in which the hemoglobin, so valuable for carrying sufficient oxygen for the needs of the body, is diminished. Such conditions are usually associated with pallor of the skin and mucous membranes, with lowered muscular tone and lack of appetite, and are often associated with slight gastro-intestinal disturbances, which in themselves may be either the result or the cause of the anemia. There is increased irritability of the central nervous system displayed by restlessness, ease of fatigue and increased rate of the heart, often associated in more marked cases with systolic murmurs and venous hum in the vessels of the neck. In older children they may complain of sensitiveness to cold, and on exertion there may be disturbances of the respiration, attacks of dyspnea and palpitation of the heart. At times there may be slight elevation of the temperature. Where the children are old enough they may complain of headache and, at times, of disturbance of vision. The urine is usually of low specific gravity, and at times slight traces of albumin are found.

Anemia of this type is usually spoken of as secondary anemia because it depends upon some primary derangement or follows some definitely known acute infection.

CONGENITAL ANEMIA

Throughout the literature one finds reference to infants who from birth show marked pallor and diminution in their hemoglobin and in the number of their red blood-cells. Ward* describes a type of congenital anemia that appears often in twins or in very weak infants, and attributes this to an insufficient share of iron deposit to tide over the period of life in which iron is found so sparsely in the diet; that is, during the period at which, normally, the infant is on milk, either breast or bottle. In premature infants this type of early anemia is very often met with. This is illustrated in the following case: A premature infant was born at the University Hospital at seven months, weighing slightly over 4 lb. Her hemoglobin ranged from 10 to 20 per cent., with a red blood count of between 1,300,000 to 2,900,000; the white count varying between 10,000 and 20,000, with an almost equal distribution between the lymphocytes and neutrophils. At

* "Bedside Hematology" (1914), Chap. 9, p. 188.

times there were found normoblasts in the circulation which varied from 11 to 33 per cent. of the total white cell count. At the age of one and one-half years this child though in moderately good condition physically still showed the same marked pallor and a hemoglobin that still ranged between 15 and 20 per cent.; her red blood cells were between 2,000,000 and 3,000,000; her white count still showed the same relation between the lymphocytes and neutrophils. At times there were from 5 to 10 per cent. of large mononuclears and transitionals and from 2 to 9 per cent. normoblasts could be found in counting 100 cells. At this time there was a marked systolic murmur and the spleen was easily palpable 4 cm. below the costal margin, with a slightly enlarged liver. The Wassermann was negative and von Pirquet reaction was also negative. This case illustrates the lack of power over a long period for the bone marrow to function normally. In such cases undoubtedly the organism compensates somewhat by a more rapid rate of flow of blood, and it may be assumed that the tissues also accommodate themselves to the lack of oxygen by taking out a higher percentage of oxygen from the blood.

Finkelstein* describes a secondary anemia which appears in infants during the first and second years which is due to a defect, perhaps congenital, perhaps due to too long feeding with milk which is low in iron. Such infants, he says, have, associated with their anemia, other symptoms of lack of development, such as lowered muscle tone and hypertonicity and are very apt to develop marked rickets. They are also very much more prone to secondary bacterial infections, especially of the respiratory and gastro-intestinal systems.

In infants, likewise, who have been nursed too long, a marked secondary anemia of this type may develop which is very refractory to treatment. Apparently in these cases a lowered power of functionating develops, probably gadually, in the blood forming organs, and it may take months or years before the normal level is reached even with appropriate diet and treatment.

The simplest type of anemia is produced by hemorrhage. Whipple, as has already been pointed out, has shown experimentally that following hemorrhage in which at least 50 per cent. of the blood has been removed, with a lowering of the blood volume in the same proportion, the return to normal under appropriate diet and treatment is very rapid. Under such conditions there is an immediate stimulation of the blood forming organs and a rapid production of red cells and hemoglobin. At first there is a very marked increase in the pulse rate, associated usually with increased nervousness and restlessness. As the blood volume, hemoglobin and red blood cells return to normal these symptoms disappear gradually. It is interesting to note that as the blood volume returns to normal, the number of red cells increases more rapidly than the hemoglobin, giving the characteristic achromia found following loss of blood. There is not only an increase during the period of active regeneration of red blood cells but also of the poly-

* Berl. Klin. Woch., No. 41 (October, 1911), p. 1829.

morphonuclear neutrophils and an equally marked leukocytosis occurs, especially during the early periods of regeneration. Along with this there is an increase in the platelets which appears more slowly but is often quite marked.

There are other signs of marked regeneration during the period immediately following hemorrhage, shown by the appearance of nucleated red blood-cells, usually normoblasts, and an increase in the proportion of reticulated red cells and polychromatophilia. Reticulated cells may increase to 7 or 10 per cent. from the normal eight-tenths of 1 per cent. to 2 per cent. As regeneration progresses these cells gradually diminish. Such are the changes which occur in a normal infant following hemorrhage, but if there has been previously present a simple anemia, or if hemorrhage is an asssociated part of some other blood disease, such as occurs in some of the hemorrhagic diseases or in diseases of the spleen, the signs of regeneration will not be nearly so marked. There may be very little or no increase in the reticulated cells. It is usually not difficult to make a differential diagnosis between conditions in which the hemorrhage is purely a primary condition and that associated with other blood diseases or which occur during the course of some acute infection. Under these conditions the signs of regeneration may be absent or even signs of marked destruction may be present, so that a careful study of the blood wherever hemorrhage has occurred is of considerable aid in diagnosis. Where there are repeated hemorrhages there is always found a lowered response by the blood forming organs and this lessened response will be greater following each hemorrhage. It will take a longer period before we find signs of regeneration. The achromia will be more marked but the reticulation and polychromatophilia will be less than in the cases in which there has been a single hemorrhage and instead of marked increase in the granular leukocytes and platelets there will be very little increase; in fact, leukopenia may exist for a considerable time and only a few nucleated cells will be found. The blood-cells will also often show a greater variation in their size and shape in these chronic cases of simple hemorrhage.

The appropriate treatment for anemia due to hemorrhage is first, of course, to find the source of hemorrhage and stop it. Assuming that this is done, the next consideration is the question of the amount of blood lost. It has been shown, especially by Robertson and Bock,* that it is often unsafe to rely on the average estimation of the amount of blood lost during traumatic wounds. The estimation of blood volume is most important, as it is the reduction in blood volume more than the reduction in red blood-cells or hemoglobin that determines the immediate outcome. Where the loss of blood has been between one-third to one-half the total volume of blood, immediate transfusion is indicated. The amount transfused, however, should be somewhat less than the amount lost. It has been pointed out that in plethoric conditions the bone marrow does not functionate as well as when there

* Jour. Exper. Med., xx (1919), pp. 139, 155.

is a slight stimulus to the bone marrow due to a slightly reduced blood volume. If the amount of blood lost does not amount to one-third of the total blood volume and the condition of the child permits, fluid taken by mouth will very rapidly replace the blood volume. Subcutaneous injection of salt solution or giving salt solution by rectum does not replace the blood volume nor is it as permanent, for some reasons, as that taken by mouth. A substitute for blood transfusion is the transfusion of gum acacia in 6 per cent. solution. This will increase the blood volume and at the same time hold the blood volume at a higher level than simply the transfusion of salt solution which only remains in the circulation for a relatively short time. The intravenous injection of salt solution, therefore, should only be done where there is a comparatively small loss of blood and in cases in which the general condition of the patient indicates that the blood volume will return to normal rather rapidly.

The general treatment of such cases demands absolute rest. If the child is restless, morphine should be given and if necessary should be repeated until the physiological condition, complete rest, is obtained. It is equally important to see that the diet contains the essentials for rapid blood regeneration. Where the child is old enough, meat should be given and in all cases vegetables, especially spinach, should be forced in the diet. Warmth, not to the point of causing increased perspiration, which usually occurs following hemorrhage, and which occurs easily in anemic conditions generally, should be guarded against, as by excessive perspiration often as much fluid is lost as can be imbibed or given by artificial means. The intake of fluid should be carefully measured and the output in urine carefully estimated, as well as an approximate loss by perspiration. In the continued treatment of the anemia following hemorrhage, which may last from several weeks to several months, rest and diet should be carefully watched. Where the blood examinations show that regeneration under this treatment is progressing satisfactorily it is doubtful whether the administration of iron would accomplish very much, though in our present state of knowledge regarding the value of iron in anemia it is probably safer to administer iron. In older children the administration of freshly prepared Blaud's pills, from 2 to 5 gr. three times a day, is suggested as the best preparation for administering iron. In younger children and in older children where Blaud's pills are not well taken or are difficult of administration, the hypodermic administration of citrate of iron, 1 to 3 gr. daily or at intervals of two to three days, or the injection of cacodylate iron may be given; though experimentally, Whipple, in this type of anemia, has not found that the administration of iron contributes to the regeneration of the blood.

Anemia, that is, a reduction in the number of red blood-cells and hemoglobin, occurs during the course of most acute and chronic infections. Such anemia following the course of known disease or infection, is termed secondary anemia. The blood picture under these conditions varies considerably. The striking pictures of blood regeneration

that follow hemorrhage are usually lacking, and the processes of regeneration are considerably slower and less manifest at any one time. There is usually a very much more marked reduction in the hemoglobin than in the number of red cells, so that there is a definite achromia usually present which varies according to the intensity of the anemia. In such cases the pallor is often more marked than the blood count and estimation of the hemoglobin would indicate. Usually the bone marrow in such cases shows a simple hyperplasia and yet the blood picture denotes a lack of red blood-cells reaching the circulation. This deficiency therefore is not due to lack of production but of delivery of red blood cells to the circulation. Just what causes this lack of delivery is not clear. In certain conditions, such as acute or chronic infections (streptococcus, probably due to action of streptococcus hemolyticus or viridans, in nephritis and in such poisons as lead poisoning), we also see signs of blood destruction, though rarely ever to such a degree as that found in pernicious anemia, and the blood picture and color index are usually entirely different. In such infections as malaria or poisons, as lead, the destructive process justifies the conclusion that there is a hemolytic action associated with certain infectious processes and poisons.

In the secondary anemias, therefore, we have often the combination of a lack of or lowered functioning power of the bone marrow and varying grades of blood destruction going on together, and the blood picture will vary according to which one of these is more marked at any one time; so that the study of the blood may show a process either predominantly destructive or due mainly to a disturbance in function or power to deliver red blood-cells to the circulation. These two processes vary not only quantitatively but qualitatively often in the same case. In certain acute infections the anemia progresses so rapidly that it is hard to explain the onset as due entirely to diminished function. In such cases, in the early stages at least, blood destruction must play an important rôle. The continuation of the anemia from initial infections is usually more dependent upon a lowered function of the blood-forming organs rather than upon the blood destruction. In fact, our methods of estimating the equation between diminished blood formation and destruction are not far enough advanced for us to be always in a position to state whether one or the other predominates, and in the lesser grades of blood production our methods may not be advanced enough at present to be able to detect at the same time low grades of blood destruction. In most secondary anemias, however, of any length, the diminished activity of the bone marrow is probably the more dominant factor in the production and continuation of the anemia.

The blood volume in these secondary anemias is usually decreased, though this is not always the case, and the hemolytic reading in cases in which the blood volume is normal or nearly normal will always show an absolute diminution in the red cell volume and relative increase in the plasma volume. There is always greater decrease in

the hemoglobin than there is in the number of red cells. Achromia and a lowered color index are always present. There is usually, however, an increase in polynuclear cells and in platelets, which indicates the activity of the bone marrow and differs entirely from conditions in which there is a partial aplasia of the bone marrow. The red cells vary in size far more than they vary in shape. Macrocytes rather than microcytes are typical of such a change. The platelets are usually materially increased, though as stated, in chronic hemorrhages the blood platelets may not be very much increased over the high normal counts.

The symptomatology of such cases of secondary anemia is usually associated with the condition which is causing the anemia and will depend entirely upon the severity of the primary cause. There is usually loss of appetite, lowered tissue turgor, easy fatigue and increased sensitiveness to cold. If the anemia is very marked, signs of edema may be present. Usually associated with any marked degree of anemia there are gastro-intestinal symptoms, which may be very marked. The physical findings do not usually show anything very characteristic beyond the pallor, diminished tissue turgor, rapid feeble heart and often hemic murmurs, systolic in time, and diminished systolic blood pressure.

The characteristics of the blood picture have already been noted: diminished hemoglobin and probably red cells, achromia, also lowered color index, variation in the size of red blood-cells, slight to marked leukocytosis and a variable increase in the platelets.

The prognosis of such secondary anemia depends almost entirely upon the primary cause of the anemia. In anemia itself, besides the measures carried out for the primary condition, diet is probably of most importance. A high protein meat content, where not contraindicated by the primary condition, and the vegetables that stimulate the output of the bone marrow, are to be forced. Transfusion, in grave secondary anemias due to infection, has not been followed by very satisfactory results. The aid is only temporary, but is indicated where the secondary anemia is grave, with a hope of tiding over a critical condition. The result of such transfusions is usually short-lived. Large quantities of blood should not be transfused as the blood volume is not very greatly diminished, and, as has been pointed out, a plethoric condition of the blood is not conducive to the delivery of red blood-cells to the circulation, so that small transfusions, if transfusions are to be given, are rather to be given than large ones. The administration of iron is problematic. Clinically, freshly made Blaud's pills, injection of iron citrate or cacodylate of iron apparently do affect the rapidity with which the lower grades of anemia are overcome. Further, we know from experimental work that there is a greater stimulation to the formation and discharge of red blood-cells during periods of marked anemia than when the level is considerably higher though below normal. Many such cases of secondary anemia apparently strike a somewhat lower level of red blood-cells and hemoglobin than

normal and continue at this level over long periods notwithstanding the administration of iron and other measures. Rest and proper diet apparently affect this particular level of abnormality just as satisfactorily as when combined with the administration of iron. The prognosis depends usually more upon the primary condition than on the grade of anemia. With the satisfactory recovery from the primary infection or intoxication, recovery is usually assured though the anemia may persist for months after the primary condition has disappeared or ceased to act as a cause.

Clinical cases that illustrate some of the points discussed in connection with secondary anemia due to acute or chronic infections:

C. P., U. of C. Hospital, 10,989, aged 14 years, gave a positive family history of tuberculosis. The child had been subject to frequent gastro-intestinal disturbances until 11 years of age. During the past two years she has had epistaxis; and during the past three years she had had hematuria which occurred intermittently, lasting from a period of a few days to weeks. Polyuria was invariably present even when the hematuria was absent. When she entered the hospital she was having an especially severe attack of hematuria which had lasted for two weeks. Her physical examination showed her thin and very anemic, with dry skin, carious teeth, cryptic tonsils and definite signs of tubercular involvement in the apices and also very definite bronchial gland involvement throughout and a generalized adenopathy. The lower pole of the right kidney could be felt and the liver was slightly enlarged. The spleen was not felt. Von Pirquet reaction was markedly positive and tubercle bacilli were found in the urine. Phenolsulphonephthalein was found repeatedly to be as low as 10 per cent. in the first hour, 20 per cent. in the second hour, extending over a period of 72 to 96 hours.

The blood picture was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Mar. 14.....	45	3,904,000	12,000	65	3.0	0	24	8.0
Mar. 19.....	45	3,456,000	12,000					
Mar. 26.....	45	4,096,000	14,100	77	0.0	0	14	9.0
Mar. 29.....	50	3,920,000	15,400	78	0.5	0	15	6.5

This illustrates the fact that the hemoglobin is very much more affected than the number of red blood-cells where there is any chronic infection with chronic loss of blood. There is a slight increase in the number of white cells but the relation between the neutrophils and lymphocytes is definitely altered and instead of the marked increase in lymphocytes which one expects in tuberculosis there was a definite decrease. In acute miliary tuberculosis this reversal is often more marked as shown in the following case:

A boy, four years old, was admitted to the hospital (U. of C. Hospital, No. 2686) with a very marked anemia. The only other symptom which his parents gave was that he had a marked cough and lately there had been increasing loss of appetite and irritability. His physical examination showed marked changes throughout both lungs, both at the apices and at the bases. His liver and spleen were both slightly enlarged and just palpable. His von Pirquet reaction was negative. X-ray showed definite miliary tuberculosis. His blood picture showed a hemoglobin of 53 per cent., red blood cells, 3,648,000; white cells, 13,800; neutrophils, 81 per cent.; eosinophils, 0 per cent.; basophils, 0 per cent., lymphocytes, 5 per cent. and large mononuclears and transition cells, 14 per cent.

The following case illustrates the long continued infection which does not show a very marked anemia. The reduction in hemoglobin over that of the red cells is manifest and the reversion of the differential count with a definite increase in the large mononuclears and transitionals.

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Dec. 27.....	65	3,560,000	16,200	59	2.0	1.0	23.0	14.0
Jan. 4.....	42	3,152,000	9,500	58	0.0	2.0	28.0	12.0
Jan. 7.....	50	3,460,000	9,200	52	0.0	0.0	38.0	10.0
Jan. 9.....	58	4,080,000	9,610	50	0.0	0.5	38.5	11.0
Jan. 18.....	54	4,256,000	11,600	50	0.0	0.5	30.5	19.0
Feb. 1.....	52	4,440,000	19,800	75	0.0	2.0	12.0	11.0
Feb. 8.....	48	3,848,000	9,800	68	1.0	0.0	23.0	8.0
Feb. 12.....	50	3,800,000	10,900	58	0.0	0.0	33.0	9.0
Feb. 27.....	42	4,200,000	10,600	54	0.5	0.0	38.0	11.5
Feb. 28.....	48	4,500,000	20,000	79	0.0	0.0	14.0	7.0
Mar. 24.....	62	4,056,000	10,700	57	4.0	1.0	28.0	10.0

Diagnosis of post scarlatinal fever was made from the history of the fever preceding and during the hospital stay, the associated streptococcic infection, the swollen lymph nodes, the slight otitis of the right ear, the desquamation which was still incomplete when he was first seen at the hospital, and the albuminuria which was the most persistent of all the urinary signs. A functional myocardial insufficiency was indicated by the late systolic murmur, and the diminished tonus shown in the heart sounds. The lung signs indicated an accompanying diffuse bronchitis. A slight degree of secondary anemia persisted throughout the nine weeks of study of the case, the reduction in the red cells and elevation in the number of white cells occurring as an accompaniment of the infective condition and malnutrition.

On the other hand, the return to almost normal of the hemoglobin and red cells can occur even in fairly acute infections as shown in the following case:

Mary M. (U. of C. Hospital, No. 9534) came to the hospital for seven weeks in July, 1915. She had spent several years in an orphange, having been abandoned by her parents. She had had mumps, chicken-pox, and frequent sore throats. Two weeks before entry she had had an unusually severe sore throat followed in one week by acute articular rheumatic fever in the right knee and ankle. Physical examination showed her to be a well developed and nourished child. The skin was rather sallow, and slight cyanosis was noted in the mucosæ. The superior lymph nodes of the neck were hard, palpable and discrete, and the tonsils were enlarged and cryptic. The chest showed an old rachitic contour, and Harrison's groove was present, while the lung sounds were slightly impaired in the interscapular areas, and a few coarse râles were heard in the primary bronchi. The heart was the chief feature of interest in the physical examination since it was enlarged to a point 1.5 cm. to the left of the nipple line, in the fifth interspace, and a soft systolic murmur was heard in the mitral area, transmitted to the second interspace. The right knee joint was still somewhat larger than the left. The temperature on entry was 39.6°C., but it fell again in two days to 38°C., and thereafter the fluctuations did not rise above 38°C. The blood examination showed:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
July 9.....	55	3,496,000	15,600	83	0.4	0	9	7
July 21.....	60	4,520,000	13,200	65	1.0	0	27	7
Aug. 13.....	85	4,944,000	9,800	69	1.0	0	18	11
Aug. 20.....	78	4,445,000	9,600	70	1.0	0	21	8

The diagnosis of acute rheumatic endocarditis is clear. The marked anemia with which she entered during the heighth of the infection disappeared almost completely in a period of three weeks. There was no treatment for the anemia beyond that of rest and diet. The only medications were salicylates during the first few days of the acute arthritis.

On the other hand, anemia following rheumatic infections may continue for months, as in the following case:

George A. (U. of C. Hospital, No. 8032) aged nine years, was a case of chronic rheumatic infection, having a history of chronic endocarditis with acute myocarditis and pericarditis. His blood picture during a period of observation for five months was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Oct. 8.....	55	4,556,000	17,700	68.0	5.0	0.0	22.0	5.0
Oct. 14.....	52	4,056,000	14,600	76.0	1.0	0.0	11.0	12.0
Oct. 18.....	48	5,072,000	16,500	63.5	3.0	0.0	25.0	8.5
Oct. 22.....	57	4,564,000	12,400	65.0	1.0	0.0	21.0	13.0
Nov. 4.....	54	4,460,000	15,800	64.0	1.0	0.0	25.0	10.0
Nov. 16.....	40	5,120,000	10,000	46.0	0.0	1.0	33.0	21.0
Dec. 1.....	59	5,360,000	15,900	57.0	1.0	0.0	31.5	10.5
Dec. 16.....	60	4,576,000	9,400	63.0	3.0	1.0	14.0	17.0
Jan. 6.....	70	4,384,000	10,200	61.0	0.0	0.0	30.0	9.0
Jan. 19.....	69	5,504,000	10,600	64.0	0.0	0.0	21.0	15.0
Jan. 27.....	72	4,864,000	11,240	53.0	1.0	0.5	30.5	15.0
Feb. 2.....	58	5,360,000	18,600	75.0	0.5	0.5	18.0	6.0
Mar. 4.....	50	4,456,000	19,000	82.0	0.0	0.0	11.0	7.0

SECONDARY ANEMIA DUE TO MALNUTRITION AND POOR HYGIENE, ESPECIALLY IN INFANTS

During infancy and childhood we often find a simple chronic anemia associated with chronic intestinal conditions. Athreptic infants will show a diminished blood volume, often as low as 50 per cent. of normal. This reduction in blood volume indicates, as Marriott* has pointed out, "that a very considerable destruction of the blood must have occurred along with the breakdown of other parts of the body. With the decrease in blood volume there is also very marked diminution in volume flow which is often less than one-fifth,

* Amer. Jour. Dis. Child., xx (Dec., 1920).

sometimes as little as one-tenth of the normal. There is a marked difference in the number of red blood-cells and in the amount of hemoglobin found in the venous and capillary circulation due to the concentration of the capillary circulation. The corpuscular concentration in the capillary blood is not infrequently as much as 20 per cent. over the venous blood."

Boycott and Chisholm* have shown in a series of experiments on under-feeding that the blood is not changed from its original condition and that the blood does not waste in parallel with the other tissues. The total loss in weight in their animals was such that some material waste of important tissues may be assumed. They do not think that the body feeds on its red cells during protein starvation. It is highly improbable, however, that during starvation many fresh red cells are produced.

In athreptic infants, due to prolonged under-feeding, a negative nitrogen and mineral salt balance appears which lowers their tolerance for food so that even the basal energy requirements cannot be met. Marriott, from the clinical study of athreptic infants and his experiments on rabbits, feels, on the other hand, that there must be some blood destruction to account for the lowered blood volume. In his animal experimentation he finds that "the blood volume was almost uniformly regained before any weight increase was observed" after food was given. During this early period of feeding the weight remained stationary. The blood volume and the volume flow started up before the weight increased. The majority of his animals regained their normal weight, but "in a few the normal volume of the blood was not regained and all of these did badly. The weight curve remained stationary and ultimately fell. All of these animals died. These experiments serve to emphasize the importance of blood volume in relation to nutrition and lead one to suspect that the 'period of repair' observed in the cases of infants convalescing from athrepsia is a period during which the reconstruction of blood volume is occurring. Once this has been accomplished improvement is likely to be rapid and steady. If the blood volume is not regained the prognosis is poor.

"The blood volume of athreptic infants decreases along with atrophy of the rest of the body. The blood volume decrease in itself leads to severe symptoms and seriously interferes with the nutritional processes. The blood volume contents become restored during the 'period of repair' and are generally restored before the restoration of other parts of the body. Anything that would shorten this 'period of repair' should favorably influence nutrition. Repeated blood transfusions and intravenous injection of colloidal solutions, such as gum acacia, result in an increase in blood volume and volume flow and are therefore indicated."

During athreptic conditions, as Utheim† has pointed out, the protein in the blood is markedly diminished. The protein percentage in

* Jour. Path. and Bac., xvi (1911–12), p. 263.

† Amer. Jour. Dis. Child., xx (Nov., 1920).

marked athrepsia may be as low as 3.94 per cent. and usually varies between 4.50 to 5.75 per cent. as compared with the normal averages of 6 to 6.5 per cent. In such cases the blood picture shows a marked achromia; change in the shape of the red cells, poikilocytosis and anisocytosis are at times quite pronounced. We have lately seen a case in which the stippling was increased to quite a marked degree and reticulation was present in from 7 to 10 per cent. In such a case both regeneration and destruction undoubtedly were going on together. In children after the second year we rarely find such extreme blood changes due simply to malnutrition. In these older children the type of anemia is far simpler, though the low level which apparently the bone marrow has struck is often held for many months after the child has regained its normal weight. Usually, however, they do not regain normal vigor until their blood picture is practically normal, both as to number of red cells and hemoglobin content. In these older children there are fewer signs of blood destruction.

Undoubtedly there are various grades of reduced blood formation and destruction. There will be marked achromia and a low color index with slight variations in the size and relatively little in the shape. The cells on the whole will be slightly smaller than normal. In these cases there is often a slight leukocytosis and a slight increase in the platelets. Neither in the athreptic cases nor in cases of milder intestinal disorder in infants and older children is there alteration in the bleeding time and coagulation time. Apparently the platelet function in such intestinal disorders is not affected; in fact, due to the hyperplasia of the bone marrow which is the common finding, there is an actual increase in the output of platelets, though, as stated before, just why there is a diminished output of red blood cells is not clear. In very severe cases of malnutrition in older children blood findings resembling those of athreptic infants are found. In such cases there will be very much more change in the red cell picture, and variations in size with large cells as well as small cells will be found associated with changes in shape. Nucleated red blood cells may also be present. If they are, there is usually a diminution in the leukocytes and platelets. In such cases the color index may approximate 1 and the picture and the blood resemble somewhat that of pernicious anemia. This is especially true in cases of malnutrition associated with syphilis. In such cases the blood picture will be very puzzling, and apparently the hematopoietic tissue reverts to its embryonic state. At times the cause for such an anemia is not found and then the question arises as to whether this is due to congenital deficiency in the blood forming tissue. They certainly are not cases of pernicious anemia though they may resemble the blood picture of this condition very closely. The blood picture may continue for long periods in this state of chronic anemia. The children apparently get along fairly well. It appears that they have accommodated themselves to the lower functioning level of the bone marrow and at times it seems almost impossible to restore the normal level of blood formation. Where a cause can be

found that might explain the condition this, of course, must be removed or remedied. Even when this is apparently done it is often very difficult, if not impossible, for the blood forming organs to regain their normal level. Therapy, other than proper hygiene, rest and increase of the dietary factors which assist in blood regeneration, rarely does any good. Even these dietary measures, as has been pointed out by Whipple, have very much less effect than in acute anemias. It is important, therefore, in all secondary anemias to pay especial attention to the dietary factors. Iron, as indicated in the other secondary anemias, may be tried, though in these chronic cases it will rarely have any effect. Blood transfusion, as suggested by Marriott for athreptic infants, may also in older children, especially with very marked anemia, have a definite though temporary beneficial effect. It may stimulate the bone marrow to a higher level of functioning even though this level may not reach up to the normal.

Clinical cases illustrating some of the blood conditions found in simple chronic anemias:

C. M., aged four months (U. of C. Hospital, No. 9704), was a case of typical athrepsia. Her von Pirquet and Wassermann reactions were negative. The blood picture over a period of two months was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitional cells	Myelocytes
Aug. 12....	50	3,688,000	12,700	35	0	1	61	3	0
Aug. 26....	60	4,120,000	10,600	26	0	3	62	5	4
Aug. 30....	60	4,120,000	12,600	28	0	1	62	6	3
Sept. 10....	65	4,220,000	11,850						
Oct. 10....	70	4,250,000	12,000						
Oct. 21....	75	4,390,000	12,450	30	1	1	57	8	3

It will be seen in this case that the hemoglobin reduction was far more marked than that of the red cells. The white count was practically normal and a few myelocytes were found. There were no nucleated red blood-cells.

L. W., aged three months (U. of C. Hospital, No. 8462), was a typical athreptic infant. Her skin was dry and waxy with very greatly impaired tissue turgor. Her luetin, von Pirquet and Wassermann tests were negative. Her blood picture over a period of two months was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Dec. 29.....	50	2,904,000	6,800	63	1.0	0	32	4.0
Jan. 5.....	48	3,420,000	9,000	55	1.0	0	39	5.0
Jan. 12.....	50	3,900,000	.....	45	1.0	0	40	14.0
Jan. 25.....	58	.....	10,800	46	0.0	1	43	10.0
Feb. 16.....	40	4,008,000	9,200	40	0.5	1	49	9.5
Feb. 19.....	40	3,450,000	6,440	55	1.0	0	38	6.0

During this period her general condition improved, though as is seen her blood returned very much more slowly to normal. Though the red cells increased considerably her hemoglobin was somewhat reduced, this notwithstanding the fact that her general condition and weight were steadily upward.

E. E., aged 19 months (U. of C. Hospital, No. 8610), had had whooping cough and mumps at 16 and 17 months followed by marked malnutrition. He was very pale and apathetic; the mucous membranes were slightly cyanosed, and there was slight edema of the extremities. The lymph nodes throughout were slightly enlarged. Both liver and spleen were slightly enlarged and could be easily palpated 2 to 3 cm. below the costal margin. Von Pirquet, luetin and Wassermann tests were negative, as were all the urinary tests and kidney function tests. The dietary history of this child had been poor as his diet had consisted mainly of milk, cereals, bread and butter, and potatoes. His blood picture is as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Jan. 22.....	25	3,712,000	9,800	45	0	0	37	18
Jan. 25.....	38	3,800,000	9,720					
Jan. 26.....	40	3,620,000	11,600	56	0	0	33	11
Jan. 27.....	44	3,280,000	11,000	54	0	0	31	15
Feb. 5.....	48	4,512,000	9,200	40	3	0	38	19

It shows the rapid response to treatment up to a certain level. This child, besides receiving the regulation anemia diet which is rich in meat protein and in blood forming vegetables, received every third day subcutaneous injection of $\frac{5}{10}$ c.c. of citrated iron.

The following case illustrates the marked secondary changes which occur in a newborn infant due to a toxic drug action during the course of which an acute infection produced only a slight blood reaction with an increase in the polymorphonuclears:

No. 8048A. A baby girl, born prematurely at six and one-half months, weighed at birth 2140 gm. By the fourth day the weight had fallen to 1860 grams, but was followed by an increase of 20 gm. per day. Birth weight was recovered by the fourteenth day, and on the twenty-eighth day she weighed 2280 gm. Feeding until she was 28 days old consisted of pumped breast milk; from that time until hospital entrance, of a mixture of breast milk and Schloss' formula. She was 40 days old when she entered the hospital, having been sent there to escape contact with the children at home who had pertussis. She was under observation for 27 days. Physical examination on entry to the hospital showed a small, well-nourished baby. The anterior fontanelle was open and level, its diameter four times 6 cm., while the posterior fontanelle was nearly closed. All other physical signs were likewise normal. The normal physical signs and normal development continued for 10 days, at which time an error on the part of a new druggist occurred. He substituted potassium chlorate for potassium chloride in the milk formula, and on the twelfth day after entry a marked septic picture was presented, which was not dispelled until the nineteenth day after entry. At discharge on the twenty-seventh day the normal progress was thoroughly reinstated. The physical signs of the septic picture were cyanosis, jaundice of the scleræ, dyspnea, vomiting, diarrhea, an increased temperature, which on Nov. 20 rose as high as 40°C., and a slight dulness in the left infra-clavicular region, accompanied by a slight bronchial breathing on the left side. The septic

blood picture was followed closely, the main features noticed between Oct. 9–17 (normal) and Oct. 19 (potassium chlorate) being the sudden drop of the hemoglobin from 80 per cent. to 30 per cent. and the loss in red cells, 5,312,000 to 2,856,000. There was also an increase in the number of the white blood-cells from 8200 to 15,850, and a marked increase in the relative numbers of polymorphonuclear neutrophils. To this change in the normal constituents of the blood was added the production of immature forms, normoblasts being noted from Oct. 20 to Oct. 26, accompanied by anisocytosis, poikilocytosis, pallor of the red cells, and occasional stippling of red cells.

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Oct. 9.....	80	5,312,000	8,200	35.0	2.0	0.0	56.0	7.0
Oct. 19.....	30	2,856,000	15,850	55.0	0.0	1.0	33.0	11.0
Oct. 20.....	30	1,920,000	18,200	34.0	1.0	0.0	50.0	15.0
Oct. 21.....	25	1,804,000	15,980	52.5	3.5	1.0	25.0	18.0
Oct. 22.....	27	2,270,000	16,300	54.0	1.0	3.0	27.0	15.0
Oct. 23.....	38	2,550,000	16,250	50.0	1.0	1.0	31.0	17.0
Oct. 25.....	39	2,480,000	27,400	48.0	3.0	2.0	28.0	19.0
Oct. 26.....	40	2,760,000	24,800	50.0	2.1	1.5	29.2	18.2
Oct. 27.....	35	2,560,000	18,500	45.0	1.0	1.0	37.0	16.0
Oct. 28.....	40	3,550,000	14,400	30.0	0.5	0.0	59.0	11.0
Oct. 31.....	48	3,895,000	8,700	43.0	1.0	0.0	48.0	8.0
Nov. 2.....	50	4,210,000	8,900	46.0	0.5	0.0	45.0	8.5

In this case both blood destruction and blood regeneration can be followed from the normal picture of entrance. The destructive action of the drug is clearly evidenced in the blood picture followed by signs of marked regeneration.

CHAPTER LXXVII

THE ANEMIAS

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CHLOROSIS

Chlorosis is a blood condition which appears in girls between the age of 15 and 25 years. Age is an important factor. It is most likely to come on at the time of the beginning of the functioning of the genital organs, especially the internal secretion of the ovaries. The menstrual periods often become irregular or there are other menstrual disturbances in, according to von Noorden, as high as 72 per cent. of the cases. At times there is found to be hyperplastic development of the genitals. There is often a family history of chlorosis in the mother or in more than one of the same family, especially in large families. The etiology of the disease is unknown. There is comparatively little known about the pathology of the disease since the condition is rarely fatal. The blood picture merely shows a slight diminution of the red blood-cells with a low percentage of hemoglobin and with an increase of the plasma. Haldane and Smith* in their studies on chlorosis point out that where the hemoglobin per cubic millimeter was less than 50 per cent. of the normal, the blood volume was increased in proportion to the severity of the disease and the oxygen capacity, or total amount of hemoglobin, was approximately normal, that is, 95 per cent. of normal. They say that chlorosis should be considered rather a condition in which there is a great increase in the plasma of the blood, the apparent loss in the hemoglobin being due almost entirely to the increase in plasma. The specific gravity of the plasma in chlorosis is normal so that the increase in volume comes entirely from a surplus of normal plasma. It is therefore a quantitative rather than a qualitative change in the plasma. Why the plasma is increased is not known. If we take into account that the total blood volume is increased with almost a normal number of red cells in the ordinary count, it is clear that there is really a large increase not only in the red but also in the white cells and in the platelets. If the plasma were not increased, we would really get a very marked increase in the red blood counts. In some cases Haldane and Smith say that this would be as high as 8,000,000 per cubic millimeter. This is due to one of two factors; either an excessive formation of the red blood-cells or a diminished destruction

* Jour. Physiol., xxv (1899–1900), p. 331; and Smith, J., Trans. Path. Soc., London, li (1900), p. 311.

of the red blood-cells. There is no evidence of increased red cell destruction. The easiest assumption would be that the number of red cells is a compensatory act on the part of the hematopoietic system. This compensation, however, does not extend far enough, for the hemoglobin per cell is markedly decreased though the total oxygen capacity is almost normal due to the increased number of red blood-cells. It has often been noted that during the treatment of chlorosis if recovery is rapid a moderate leukocytosis will appear. This is undoubtedly due to the fact that as the blood concentrates there is a temporary leukocytosis which depends upon the length of life of these cells, so that instead of a slight reduction in leukocytes which is normally found, there is really an increase in their number. In the same way the increased number of lymphocytes may be accounted for, as has been suggested by Ehrlich, by an increased flow of lymph which, in a mechanical fashion, washes the cells out of the lymphatic tissue.

Haldane and Smith have pointed out a very interesting fact regarding the use of iron. In cases in which improvement occurs speedily following treatment of iron they found that there was rarely any increase in the total amount of hemoglobin and, as they comment, "recovery affords no ground for assuming that iron is built up into hemoglobin." In fact, the total amount of hemoglobin was found to be approximately that of uncured cases. Refractory cases, that is, cases which do not respond to iron, were those in which there was a need of an increase in hemoglobin. They conclude that "in typical cases the curative factor of iron salts must be exercised otherwise than simply in building up the hemoglobin. The essential process in the cure of chlorosis is the reduction in the volume of plasma."

Hagen* came to the conclusion that there were three separate stages or processes during cure which should be recognized. "During the first stage there is an increase in the number of corpuscles per cubic millimeter without any increase in the corpuscular retention of hemoglobin. In the second stage there is a further increase in the number of corpuscles and at the same time an increase in the amount of hemoglobin. During this period the number of corpuscles per cubic millimeter occasionally rises beyond the normal and in these stages a last stage occurs in which the number of corpuscles is greatly diminished while enrichment in hemoglobin continues in those remaining. This apparently anomalous fact finds an explanation in the proof already given that in chlorosis the total number of corpuscles of blood is much increased." This increase in the total number may reach as high as seven to seven and a half millions per cubic millimeter and depends upon the rapidity of reduction of plasma during the period of cure. This elevation will only continue as long as the life of the cell, that is, 15 to 20 days, unless the stimulation to the production of red cells continues as it did during the course of the disease. The increased volume of blood gives an explanation of the circulatory and respiratory disturbances which occur during chlorosis; "the large volume of blood throws

* Du Sang, p. 708, quoted by Smith.

greatly increased work on the heart diminishing the value of any given quantity of blood for respiratory exchange."

The hypertrophy and dilatation of the heart and functional cardiac murmurs can all be explained by this increased volume. The dyspnea which is characteristic of chlorosis results from the fact that "while the blood as a whole has a normal capacity for oxygen this increase in quantity renders it unwieldy as an oxygen carrier."

The blood may also be overloaded with carbonic acid and on account of the lessened amount of hemoglobin per cell the blood, as it passes through the lungs, will not be sufficiently aerated from the carbonic acid in the plasma.

Plesch studied the blood volume in two cases of chlorosis by the carbon monoxide method and found also an increased blood volume. It will be interesting to follow these observations on the blood volume by the "vital dye" method which is more accurate and gives higher values than those obtained by Haldane and Smith and Plesch, so that their explanation may not be the correct one. It will be remembered that Haldane and Smith and Plesch find the blood volume to be one twenty-first ($\frac{1}{21}$) and one-nineteenth ($\frac{1}{19}$) part of body-weight, so that by their method even increases in the blood volume over these figures would still be less than what is considered as the normal blood volume which is one-tenth ($\frac{1}{10}$) of the body-weight.

It has been suggested that the bone marow is deficient, at least in its total functioning power. This is plausible from the fact that chlorosis usually takes place during the period in which menstruation is being established. During this period a greater strain is put on the blood-forming organs. The functional weakness of the bone marrow is shown by the small size of the red blood-cells, the small amount of hemoglobin present in the blood, the lack of polychromasia and the fact that nucleated red cells are rare. The tendency to functional disability of the bone marrow during adolescence is also probably associated with other internal glandular adjustments which, as we know, are going on during this period.

Chlorosis is especially associated with bad hygienic conditions, overwork and worry. Fatigue, both mental and physical, and a lack of proper food are predisposing factors. Chlorotic girls usually give a history of preferring sweets and cakes and have a distaste for simple nutritious food. That these are the main predisposing causes is shown by the fact that by a correction of the physical, mental and nervous hygiene, with a proper diet, rest and iron, the condition is easily remedied. During this process there is probably a compensatory increase in the red bone marrow in an attempt to make up for this functional deficiency.

The symptoms usually come on gradually though they may come on very rapidly. The first symptoms complained of are usually breathlessness, fatigue, tiredness and palpitation. These symptoms are present before there is any marked pallor. The pallor is first noticed in the lips and conjunctivæ, later in the skin. The greenish color,

after which the disease is often called "green sickness," is rarely met with except when there are very marked blood changes. There is very little or no temperature unless associated with some secondary infection. Digestive disturbances are often prominent either from abnormal over-eating or from abnormal distaste for food. Constipation is common. Often there is increased acidity of the stomach and gastric ulcers may develop as complications. The most prominent symptoms are referable to the circulatory system. Breathlessness and palpitation with rapid changes in the peripheral circulation are very common. The pulse is usually fast. After prolonged exertion or exercise fainting spells are common. Edema of the ankles, especially in those who stand for long periods, is found. Heart examination shows a right-sided dilatation. Superficial cardiac pulsation is often diffuse. Cardiac murmurs are usually present and systolic in time. They are heard most frequently over the pulmonary area, close to the sternum in the second or third interspace. These sometimes are due to a lack of muscle tone. Arterial or venous hums are often heard in the jugular region. These murmurs vary considerably, being more evident after exercise, and may almost disappear after prolonged rest. Venous thrombosis is a rare complication. It is due probably to the marked increase in the number of platelets. It occurred in 6 out of 431 cases reported by von Erben and in 5 out of 230 cases reported by von Noorden. The occurrence of the thrombosis in one of the sinuses of the brain accounts for most of the fatalities which occur in chlorosis. The urine is usually increased in quantity and has a low specific gravity. Amenorrhea is common and leukorrhea is often present. Muscular weakness and nervous irritability are very common. There may be hysterical attacks, or paroxysmal headaches may be a prominent symptom. The patient is usually tired and sleepy.

Blood Changes.—The blood picture is usually characteristic. A drop of blood is pale and watery. The number of red cells is reduced to between three and four million. Hemoglobin varies between 15 and 45 per cent. which gives a very low color index, between 0.25 and 0.54. There is an increase in the lymphocytes and the proportion of large lymphocytes is often markedly increased. The red blood-cells show a change in size and shape. Poikilocytosis may be very marked but differs from that found in pernicious anemia in that the cells are small and there is central pallor. Nucleated red blood-cells are rarely found. When improvement begins, the number of red blood-cells increases more rapidly than the hemoglobin. The return of the hemoglobin content to the normal is the last step in recovery. There is, however, a tendency to relapse. This may be partly due to the fact that these patients are seldom willing to carry on treatment for a long period and as the most disagreeable symptoms disappear rapidly the patients consider themselves cured. Cases should be followed for a long period, however, because although the disease is not a fatal one it undoubtedly has a profound effect upon the normal development at a period of growth during which there is need of the

best general nutrition. This late adolescent period undoubtedly affects the future general well-being of the individual far more than is generally supposed.

Diagnosis.—The diagnosis of chlorosis is easily made. The fact that it occurs in girls during their adolescent period and is usually associated with poor hygiene or with excessive nervous or physical fatigue, along with the color of the patient and the blood picture, makes the diagnosis unmistakable. The only danger is that along with chlorosis other conditions may be associated and this is particularly true of tuberculosis. Tuberculosis occurring during the late adolescent period may show a marked anemia which may be mistaken for chlorosis. Marked secondary anemia from concealed hemorrhage may at times make the diagnosis rather difficult.

Treatment.—The treatment of chlorosis lies along hygienic and dietetic lines. Chlorosis can be more easily prevented than cured by the application of these same methods and they should be applied to all rapidly growing girls during their adolescence. Sunlight and proper hygiene, both from the standpoint of prophylaxis and treatment, are indispensable. When chlorosis is present, the amount of exercise must be regulated most carefully, care being taken to prevent fatigue; in fact, the daily régime must be worked out with this point particularly in mind. The diet must be nutritious and contain the foods which stimulate blood formation. Meat is most essential in producing stimulation. Among vegetables, spinach is very valuable in stimulating blood-forming organs. Pastries, candy, tea and coffee, or highly flavored food should be restricted or not allowed at all. It is often difficult if not impossible to take such articles out of the diet and it may be better to leave a minimum amount in the diet in order to gain the co-öperation of the patient than to cause antagonism by too strict a ruling. Simple stomachics, such as nux vomica or tincture gentian compound, either separately or in combination, are valuable aids in stimulating the appetite. Iron is of more value in chlorosis than in any other anemia. It is more often given in the form of freshly prepared Blaud's pills, from 15 to 20 gr. a day, and produces results very rapidly. The citrate of iron given subcutaneously is also very valuable. Almost any form of inorganic iron will produce results. Some prefer using organic iron and there are many preparations in the market, mainly derived from ox blood, but if one wishes to use organic iron, it is much better to give injections of human hemoglobin by simply taking human red blood corpuscles and injecting the dissolved hemoglobin either subcutaneously or interperitoneally. A very rapid return to normal can be obtained by this method as this organic hemoglobin is undoubtedly the most active stimulant to the blood-forming organs. Careful attention must be paid to whatever other symptoms are manifested. Constipation must be corrected, and this should be done by proper exercise and diet. Bulky food, such as is obtained by giving large quantities of coarse vegetables, whole wheat bread or whole wheat and bran bread, will often correct the condition

without any laxative medication. Abdominal and postural exercises will be found very beneficial. In some cases, abdominal massage may be necessary to stimulate natural peristalsis. If drugs are to be administered, the simple ones such as oleum petrolatum or some of the other bland pills may be sufficient. Cascara or aloin are probably the most widely used cathartics. Chlorosis should, under proper treatment, improve very rapidly. A few weeks will make a great difference in the appearance of the patient and the blood picture may improve very rapidly so that inside of three or four weeks it may be almost back to normal. This should be no indication for discontinuing treatment. The iron may be discontinued when the hemoglobin reaches 90 but the hygienic and dietary régimen should be continued for months; or better, the patient should be persuaded to adopt the régimen permanently. This is the best way to avoid recurrences, which, as stated, are quite frequent.

There is a type of anemia corresponding, in blood picture at least, to chlorosis in adolescents, which is found in infants and more rarely in older children. Bunge and Abderhalden have shown that a diet containing too little iron can produce in young animals a blood very similar to that of chlorosis. The French school have described chlorosis as occurring not infrequently in infants, in fact Nonat* reported a series of 68 cases with this type of chlorosis. Halle and Jolly† in 1903 gave a very good description of the blood picture in a case of chlorosis. Schwarz and Rosenthal‡ report a series of 40 cases, 29 of which occurred under one year of age. The oldest in their series were eight years of age.

The appearance of the children does not lead one to suspect the presence of anemia and they think for this reason that the diagnosis is often not made unless there is a blood examination. They say that this type of anemia occurs in the development of immature infants, twins, and those who have had a rather stormy history during the first three months of life. Fourteen of their 28 cases which occurred during the first year of age had been breast fed; 10 had had both breast and bottle, whereas only 4 had been bottle fed alone. Twenty-eight of their 40 cases were in boys and only 12 in girls. Several of the family histories showed that chlorosis had existed in the family or that there had been some other type of anemia. The symptomatology which they give corresponds somewhat to the chlorosis of adolescents—a loss of appetite or capricious appetite, constipation and intestinal derangements. This type of anemia may appear in premature, congenitally weak, under-weight infants or in those who appear to be well fed, with good adipose tissue. The color is grayish rather than whitish-yellow or waxy, and the mucous membrane pale but never excessively white. There is usually a systolic murmur. The spleen was only rarely enlarged. The blood examination showed a color index

* Traité de la chlorose, Paris (1864).
† Arch. de med. des enfants, vi (1903), p. 664.
‡ Arch. Ped., xxxvii, No. 1 (Jan., 1920), p. 1.

of between 0.4 and 0.6. The red blood-cells varied between four and five millions. There was reduction in leukocyte count ranging between 6000 and 10,000. The platelet count was between 200,000 and 300,000. The blood volume which they estimated in five cases was normal. In their metabolic studies they found that iron metabolism was reduced, there being a negative balance of iron but a positive balance of nitrogen. Nitrogen retention varied from 3 to 4 gm.

Just how much the iron balance has to do with hemoglobin is not known. It is supposed that the premature and weakling has an insufficient amount of iron deposited during fetal life. As a greater proportion of the deposit of iron occurs during the last three months of pregnancy, these infants bring into the world a diminished quantity of iron. In older cases, intestinal conditions or dietary errors may be a factor, though it would appear as if some other factor in addition to diet must be found to account for these cases.

The following two cases illustrate this type of chlorotic anemia found in young infants:

F. P., aged 15 months, U. of C. Hospital, No. 8058, was observed in the hospital during two periods, one of three weeks and a later period of three and a half

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals	Abnormal forms
First entry									
Aug. 15....	38	5,272,000	27,700	54.8	0.1	0.4	34.0	10.4	Pallor, Aniso. Poik.
Aug. 26....	32	5,208,000	19,300	56.5	1.0	1.0	37.5	4.0	Pallor, Aniso. Poik.
Second entry									
Oct. 11....	35	4,448,000	19,450	31.0	4.5	2.5	54.0	8.0	Pallor, Aniso. Poik.
Oct. 13....	32	6,800,000	20,450	34.0	1.5	2.5	57.5	6.5	Pallor, Aniso. Poik.
Oct. 18....	32	7,832,000	19,550	35.0	6.5	2.0	47.0	9.5	Pallor, Aniso. Poik.
Oct. 22....	40	6,384,000	11,700	32.0	0.0	1.0	41.0	27.0	Pallor, Aniso. Poik.
Oct. 27....	..	5,568,000	9,800	47.0	1.0	0.0	23.0	27.0	Pallor, Aniso. Poik
Oct. 30....	45	4,936,000	13,600	32.0	1.0	0.0	39.0	27.0	Pallor, Aniso. Poik.
Nov. 4.....	45	5,760,000	11,800	30.0	0.0	1.0	49.0	19.0	Myelocytes 0.7
Nov. 9.....	45	5,504,000	13,200	30.0	0.7	0.7	48.0	20.0	Myelocytes Anis. Poik.
Nov. 16....	45	6,208,000	13,400	38.0	0.8	1.0	48.0	11.0	Anis. Poik.
Nov. 18....	50	5,952,000	13,000	29.0	0.0	0.0	42.0	25.0	3 myelocytes
Nov. 21....	70	7,040,000	9,300	50.0	0.0	1.0	9.0	41.0	0
Nov. 24....	70	5,600,000	10,000	60.0	0.0	1.0	28.0	12.0	0
Dec. 2.....	50	6,400,000	14,800	51.0	1.0	1.0	28.0	18.0	0
Dec. 13....	45	6,172,000	10,520	30.0	0.0	1.0	50.0	18.0	0
Dec. 20....	55	6,304,000	10,200	31.0	0.0	1.0	28.0	39.0	0
Dec. 23....	65	6,336,000	15,800	26.0	0.9	0.0	30.0	43.0	0
Dec. 27....	60	5,228,000	12,800	26.0	0.0	0.7	41.0	32.0	0
Jan. 5.....	63	5,488,000	12,960	29.0	1.0	0.0	45.0	25.0	0

months. He was the seventh child of normal Italian parents and was born after a seven months' pregnancy. He had never been breast fed and when he entered the hospital he was still on a comparatively weak whole milk dilution formula. At 14 months he had had measles followed by otitis media. He was a pale child with marked signs of rickets. There were several furuncles over the sacral region. Wassermann and von Pirquet tests were negative. The blood picture which follows was typical, showing a high red cell count and a very greatly lowered hemoglobin. The leukocyte count was usually high. The platelets were increased slightly, averaging over 300,000. Unfortunately his blood volume was not taken:

2. F. B. (U. of C. Hospital, No. 8020), 18 months old. He was the fifth child. Two children had died in infancy. He had had measles at the age of one year. He entered the hospital on account of his anemia. His physical examination showed a pale, undeveloped, poorly nourished, irritable baby. The fontanelles were open and depressed. The lymph glands could be easily palpated. The liver was slightly enlarged. He had numerous furuncles over the extremities. His Wassermann and von Pirquet reactions were negative. His blood picture showed a normal or slightly increased count with a marked reduction in the hemoglobin. He had a moderate leukocytosis:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Oct. 5.....	30	5,610,000	13,750	67.5	1.0	0	21	10.5
Oct. 6.....	35	4,760,000	15,600	31.5	1.5	1	59	7.0
Oct. 20.....	39	5,150,000	21,160	59.0	1.0	1	34	5.0

These blood pictures correspond very closely to that of a third case of a girl of 17 who gave the history of menstruation beginning at 14½ years with profuse hemorrhage and severe pain in the lumbar and gastric regions. During the three months previous to her entry she had had acute epigastric pain which increased upon eating. She complained of frequent headaches, feeling tired and easily fatigued. The physical examination showed a fairly well developed but poorly nourished girl. Her skin, conjunctivæ, and mucous membrane were very pale. Her heart was enlarged and showed a murmur specially marked in the second left interspace. Her Wassermann and von Pirquet reactions and *x*-ray were negative. Her blood picture was as follows:

Hb., per cent	35
Red cells	4,032,000
White cells	10,851
Neutrophils	71
Eosinophils	2
Basophils	0
Lymphocytes	24
Large mononuclears and transitionals	40

During the period of observation her blood picture did not change. There had been a question of gastric ulcer but her laboratory and *x*-ray examination disproved this. She was put on proper hygienic diet measures and given freshly prepared Blaud's pills two or three times a day after meals. Three months after her stay in the hospital her blood was practically normal, her epigastric pain had disappeared and she no longer complained of headache or fatigue.

CONDITIONS UNDER WHICH BLOOD DESTRUCTION PREDOMINATES

Under a variety of conditions blood destruction plays the greatest rôle. This is particularly true of the anemias caused by acute infections, chemical poisonings and congenital or familial hemolytic jaundice, pernicious anemia and certain conditions associated with splenetic enlargement, so-called splenic anemia, Banti's disease and Gaucher's disease. These conditions will be discussed together. It must be understood that in all these types of conditions blood destruction is not the only factor that plays a definite part. Blood regeneration always is found, though the degree depends upon the rate of destruction and the intensity of the stimulus to the bone marrow which in an individual case may vary at different periods of the disease.

Some of these conditions have already been mentioned, such as the effect of chemical poisoning, benzol, potassium chlorate, and the acute infections in which we get, especially with streptococcus infections, a definite destruction of the red blood cells. In malaria, the action of the plasmodium causing hemolysis is an illustration of an infectious hemolytic disease. There are certain anemias of this type in which the cause of the hemolytic anemia cannot be found. In such cases the outcome depends on the rate of destruction and also as to the length of time which this continues. It is not always possible to ascertain this. Treatment, in such cases, should primarily be directed towards removing the cause when that is known; otherwise, general treatment directed towards combating the anemia and especially the introduction of transfusions has undoubtedly saved many lives in which there is a temporary toxin at work. If the period of destruction is not too long and the toxin can be removed, transfusion will tide over many critical conditions and will hasten recovery very materially.

CONGENITAL AND FAMILIAL HEMOLYTIC JAUNDICE

This is a condition in which there is an increased blood destruction, increased fragility of the red blood corpuscles, icterus and enlargement of the spleen. It occurs in several members of a family and evidences of it are often present at birth. As a familial disease it was first described by Minkowski who described it as occurring in eight members of one family during three generations. These cases showed a chronic jaundice with increased bile pigment in the blood serum, also urobilin in the urine. There is distinct anemia present, the red cells being diminished usually to below three millions. Chauffard showed that there was increased fragility of red blood corpuscles to hypotonic salt solutions so that this condition is ordinarily called the "Chauffard-Minkowski" type of hemolytic jaundice, though some of their cases do not have a family history but occur in infants from birth.

The acquired form of the disease was first established by Hayem, and later was fully described by Widal, so that this form of acquired hemolytic jaundice is termed the "Hayem-Widal" type. Widal pointed out that there were definite periods of increased jaundice

which he termed "crises of deglobulization." During these crises hemoglobin appears in the urine, but not bile pigment.

The etiology of these conditions is not known. Chauffard thinks that primary infections with tuberculosis or syphilis may be important etiological factors, whereas in the acquired form some acute or chronic infection is supposed to be the etiological factor. Whether the defect is primarily in the blood-cells or in the spleen is not at present clear. That the spleen plays an important factor there can be little doubt, especially since the introduction of splenectomy in certain of these cases has produced very definite beneficial results, though where the destructive process is due to an acute toxin such as in pernicious anemia, as will be pointed out, splenectomy does not show such valuable results.

The amount of hemoglobin is increased and bile pigment is present in the blood plasma. Whether this change of hemoglobin takes place in the circulation or whether it is taken care of by the liver is not clear. In this condition the bone marrow itself is not definitely damaged. At least it is able to produce red cells to such an extent that it is often able to keep pace with the destructive process for many years. The red cell count is usually two to three millions. In the congenital type, it may be over three millions; in the acquired type it is rarely under two millions. The cells show marked anisocytosis. They are smaller in size and their fragility is definitely increased. Hemolysis begins often at 0.7 and is completed at 0.46 or 0.45 salt solution instead of normally beginning at 0.44 and being completed at 0.34 to 0.36. This differs materially from secondary anemias where fragility is decreased rather than increased. Reticulation of the cells is markedly increased, often as much as 20 per cent. The hemolytic process does not affect the granular leukocytes. The leukocytes may show periods of increase especially during periods of exacerbation. The pathology of the condition shows a marked deposit of iron and blood pigment in the bone marrow, spleen, liver and kidneys. The spleen is usually enlarged due to the accumulation of red cells in the splenic pulp and sinuses. The macrophages are increased. The bone marrow shows a definite hyperplasia especially of the red cells. Due to the increased production of bile pigments and salts, gall stones are frequently found.

Diagnosis.—Diagnosis rests upon the jaundice which is never extreme, the diminished resistance of the red cells to hypotonic salt solution and the increased number of reticulated cells. The spleen, though enlarged, is never as large as it is in Banti's or Gaucher's disease. The tenacity of the condition, and the fact that in children it is usually congenital, makes the differentiation from pernicious anemia much easier in infancy and childhood than it is in adult life.

The prognosis in the congenital type is much more favorable than in the acquired type. A fairly normal life may be led by these patients for a long period though they are never up to par and are more susceptible to infections than the ordinary child.

Treatment.—There is no condition in which splenectomy shows such a favorable outcome as in these cases of hemolytic jaundice. The death rate is low, especially if the operation is performed early, and since the regenerative power of the bone marrow is not affected a normal level of blood regeneration may occur so that the condition can be considered often as cured. The results are therefore more permanent in this condition than in any other except perhaps that of Banti's disease where splenectomy is performed early. In the mildest type of cases with very little blood change or effect on the general well being, splenectomy may not be indicated. The only contrary indication for splenectomy is that it should not be performed during a period of exacerbation. In the acquired form the primary indication is to remove the cause and often where this is found recovery will result without any further interference. Of late, the results of *x*-ray treatment and radium treatment in these cases have been very much more encouraging, and where splenectomy for some reason or other is not indicated or permitted, these should be tried.

POLYCYTHEMIA

Polycythemia is a condition in which the number of red blood-cells is increased above normal. As has already been pointed out in several physiological and pathological conditions there may be a definite increase in the number of red cells and in the percentage of hemoglobin. Such conditions are found physiologically in high altitudes and pathologically when there has been a definite loss of water so that the blood becomes concentrated, as in diarrhea. In this latter condition the blood volume may be markedly decreased, mainly a loss of plasma, with relative increase in the red cells, and this is also the case in cardiac conditions, especially those connected with congenital heart diseases associated with cyanosis. In 1892 Vaquez reported a case of primary leukocythemia with chronic cyanosis and splenomegaly. This condition has been termed erythremia in true distinction to erythroblastic or secondary polycythemia such as those just mentioned. True erythremia rarely occurs in childhood. W. S. Lucas* has quoted 149 cases. No case of true erythremia as far as known has been reported before the second decade. Guinon, Rist and Simon† report a case in a child 10 years of age with polycythemia, cyanosis and splenomegaly. There was chronic jaundice and the polycythemia and cyanosis were at times transitory, and, as Lucas remarks it cannot be rightly regarded as a case of erythremia. In this case there was urobilinuria accompanying the exacerbation of jaundice. The red cells varied from 6,000,000 to 7,600,000. This polycythemia, however, fell later to 4,000,000, while a year previously it had been 3,400,000. The red blood-cells showed resistance to hemolysis above the average. This case can be considered perhaps as a chronic splenomegalic acholuric jaundice with oligocythemia. As far as polycythe-

* Arch. Int. Med., x (1912), p. 597.

† Bull. et Mem. Soc. Med. d'Hopital de Paris, xxi, series 3 (1904), p. 786.

mia is concerned it corresponds somewhat with the case of myelogenous leukemia which we have given in the section on acute leukemias. During the second decade 4 per cent. of Lucas's recorded cases were found. These were as follows:*

A school-girl aged 17. Except for measles in childhood her health had always been good. She had never menstruated. Three years before she had had a severe cough and since then been troubled by palpitation and general weakness, blueness of lips and fingers and irritable disposition. Three months previous to examination she had a fainting spell preceded by a distinct aura consisting of groaning and twitching of muscles of forehead. She lost consciousness for about five minutes and on awakening found her bedclothes saturated with blood from an epistaxis. During the next three months she had four similar attacks accompanied by distinct aura and severe epistaxis. Her skin was very dusky, lips, tongue and conjunctivæ blue. Spleen was enlarged 1½ in. below the costal margin. There were dilated veins and venules on her neck and marked carotid pulsation. Her blood pressure was 120. Skin slightly pigmented, fingers slightly clubbed and nails incurvated. Her urine showed slight traces of albumin and occasional traces of indican. Her red cell count was 5,917,500 to 7,586,000 and her hemoglobin ranged from 110 to 112. Her white cells were 4000 to 6250. Her differential count was—polymorphonuclears 64 to 76 per cent., lymphocytes 24 to 31 per cent., eosinophils 0 to 1 per cent. and transitionls 0 to 4 per cent.

The second case was that of Sandesky† of a girl of 17. She complained of a cough, expectoration, etc. Cyanosis, enlarged spleen and heart much displaced. Red cell count 6,380,000. Hemoglobin 105. White cells 8700. Normal differential.

The third case was that of Reissmann.‡ This was a girl aged 18 who for four years had had blue lips and dusky skin. Three years previously she had had attacks of unconsciousness and vomiting. She complained of frequent headaches. Irregular menstruation. She had had an attack of diarrhea and vomiting two years previously. At times her eyes became prominent. Her skin was slightly dusky and dry, her lips were blue, mouth and fauces very red. Her spleen was not enlarged. Liver dullness slightly increased upwards. There was venous pulsation in the neck. Her eyes were distinctly prominent. Von Graeffe's sign was absent; fine tremors of the hands; the thyroid gland was not enlarged. The optic disc veins were engorged and disc red. Her urine showed traces of albumin, much chromogen, diacetic acid and traces of acetone. Her blood at one time showed red cells 7,404,000, hemoglobin 124, white cells 5600. Blood very rich color, coagulation time 30 seconds, viscosity much increased. Under observation her blood count gradually went down and two years later she was well though with slight cyanosis which became pronounced on exertion, but there was no excess of red cells.

The fourth case was that of Hann.§ This was a girl aged 18 who had been well until 13 years of age. From that time on she showed retarded development. She had menstruated twice when 15 but never since. During the past two years she had had occasional abdominal pains of uncertain nature. Lues was suspected. There was no cyanosis. Spleen was three fingers length below the costal margin. Liver was not enlarged. Red cell count 6,000,000 to 7,000,000. Hemoglobin 110 per cent. Color index 0.78 to 0.91. Under treatment with iodid of iron and occasionally tincture of perchlorid of iron her condition generally improved, but the spleen remained enlarged and the red cell count was slightly increased.

* Chace, N. Y. Post Grad. Med. School (1907), p. 477; also The Post Graduate, N. Y., xxiv (1919), p. 263.

† Sandesky, Policlinco, Rome, xvii (1910), p. 611, sex. prac.

‡ Reissmann, C., Australasian Med. Gaz., xxv (1906), p. 514.

§ Hann, R. G., Lancet, London (Jan. 18, 1908), p. 160; also Proc. Roy. Soc. Med., London, Clin. Sec. (1907–8), p. 59.

From these cases it may be seen that true polycythemia is a rare condition in children and is more likely to occur in adolescent girls. The symptoms are marked by persistent absolute increase in red blood-cells and increase in viscosity and total blood volume (no estimations of blood volume, however, have been noted in these cases of children). Haldane and Smith* have reported increased blood volume in several cases and Bock and Means† report increase of blood volume by the vital red method, with which they found the total blood volume of 124 c.c. per kg. of body-weight instead of the normal of 85 c.c. and in another case a blood volume of 118 c.c. per kg. of body-weight. The increase is due almost entirely to the increase in red blood-cells and not to an increase in the plasma. There is also excessive erythroblastic activity of the bone marrow and usually changes in the eye grounds, cyanosis and enlargement of the spleen. The cyanosis may be general but it is usually more marked in the face and hands. In 83 per cent. of the cases reported by Lucas there was "some intensification of the color of the skin." The face was usually "very red" or "florid," "congested," or "plethoric." Nervous symptoms are common and seem to intensify the cyanosis. Hemorrhage is a very prominent symptom and occurs in about one-fourth of all cases. The spleen is enlarged in about 75 per cent. of all cases. The liver is not usually enlarged. There is usually some disturbance of the gastro-intestinal system, and particularly disturbances are noted of menstruation. The exophthalmia as noted in one of these cases may be a prominent symptom of polycythemia. The urine often show straces of albumin and occasional casts. It may be mistaken for a chronic nephritis. The most characteristic finding is the increase in the red cells. This increase varies considerably in the same patient at different times. It may go as high as 15,000,000. The hemoglobin is usually not as high as the red blood-cells would indicate. It usually ranges between 100 and 150. The color of the blood is almost invariably darker than normal and the viscosity is increased. The coagulation time is usually shortened. The white cells are usually absolutely increased in the majority of cases, sometimes amounting to a distinct leukocytosis. The differential count usually shows a moderate increase of polymorphonuclear cells. Atypical cells may be found occasionally. Treatment in these cases is rather unsatisfactory. Venesection is reported to give temporary relief. The best results would seem to be obtained by a carefully mapped regimen which would avoid strain and excessive physical and mental over-exertion. Radium or *x*-ray which is suggested by Hurwitz and Falconer‡ would seem to be the most rational means of diminishing the production of red cells.

Diagnosis.—Where polycythemia occurs in children it is usually due to a secondary cause and not true erythremia in which there is a constant persistent absolute polycythemia of unknown origin.

* Haldane, J. and Smith, J. L., Jour. Physiol., xxv (1900), p. 331.

† Bock and Means, Oxford Med., ii, Chap. 18, p. 767.

‡ Hurwitz, S. H; and Falconer, E. H., Jour. Amer. Med. Assoc., lxx (1918), p. 1143.

The prognosis in true erythremia is progressive towards a fatal termination.

Secondary polycythemia occurs most often in infants and children due to cardiac, congenital or aquired diseases or in chronic pulmonary conditions. In this condition as in the true erythremia there is an increase in the blood volume associated with absolute increase of red blood-cells and percentage of hemoglobin. The specific gravity and viscosity of the blood is high. There is undoubtedly hyperactivity of the bone marrow. There is, however, in this condition, an unequal distribution of the red cells, the cells being very much more numerous in the venous and capillary circulation than in the arterial. The following case illustrates the type of polycythemia found in a congenital cardiac case:

Hospital No. 2493. Peter D., aged 15 years. Family history was negative. At birth he was cyanotic and had always been so. He became dyspneic on exertion. Complained of headache and dizziness and had occasional attacks of vomiting. His vision was clouded. At times he had vomited blood. His physical examination showed a well developed boy. His skin and all mucous membranes were markedly cyanotic. Examination of heart showed a marked systolic murmur all over the precordia, with a definite systolic thrill. The murmur was especially marked over the tricuspid and pulmonic areas. The arterial walls at the radius were firm, palpable and somewhat irregular. His liver and spleen were somewhat enlarged. Fingers were clubbed. Blood pressure was S. 102, D. 79. His red count and hemoglobin were as follows:

Date	Hb., per cent.	Red cells
March 4	138	8,160,000
March 10	110	5,440,000
March 11	140	6,328,000
March 11	130	6,904,000

His white count was slightly increased, averaging 14,000; his differential was normal.

The diagnosis in such cases is usually comparatively easy and treatment depends upon the primary condition. There is no special treatment though under special conditions venesection or *x*-ray treatment might be indicated.

Means and Newburgh* have studied two cases of polycythemia associated with mitral stenosis. They found that the basal metabolism was not increased. The pulmonary ventilation, however, was markedly increased, being 9.4 and 9.5 liters of air per minute. The volume output of the heart per beat was only 27 and 17 c.c. against the normal control of about 50 c.c. and the "coefficient of utilization of oxygen" was very high, showing that an excessive proportion of oxygen was being used.

* Means, J. H. and Newburgh, L. H., Trans. Assoc. Am. Phys., xxx (1915), p. 51.

PERNICIOUS ANEMIA

Pernicious anemia is a very rare condition in childhood, there being only 56 reported cases in the literature and in more than half of these cases, 32, the anemia was supposed to be caused by intestinal parasites. Bothriocephalus and tenia and, in one case, round worm have been the intestinal parasites at fault. Only two infants have been reported with blood pictures resembling pernicious anemia. D'Espine* reports two cases, one 7½ months, one 11 months. It is doubtful whether these are true cases of pernicious anemia as they both recovered with the use of hematopoietic serum. We recognize the fact that primary anemias of infancy and childhood tend to be more rapidly fatal than in adult life. Morse and Wohlbach† report the history and autopsy findings of a case of pernicious anemia in a boy, which began at the age of 5 years and ended fatally 3 years later. During this period his hemoglobin had varied from 28 per cent., when he was 6½ years, to 10 per cent. shortly before his death. His red cells varied between 1,600,000 and 570,000. His white cells remained around 8000. The differential count, as given by Morse in his case was: Small mononuclears 61 per cent., large mononuclears 11 per cent., polynuclear neutrophiles 25 per cent., eosinophiles 0.5 per cent., basophiles 2.5 per cent. There was marked variation in the size and shape of the red cells with a tendency to the predominance of the larger forms. Neither stippling nor achromia were pronounced. The blood platelets were down to 12,900. Ten normoblasts and one megaloblast were seen to each 200 white cells. The autopsy gave the typical findings of pernicious anemia. All the lymph nodes were enlarged and yellowish in color with reddish centers. The spleen was deeply injected. The malphigian corpuscles were of fair size. The reticular tissue of the pulp was reduced in amount and only contained a few lymphocytes but many mononuclear and polynuclear eosinophiles. In the sinuses, were small groups of myelocytes and occasional nucleated red blood-cells. The liver showed a small amount of brown pigment. The kidneys showed the same brown granular pigment in the epithelial cells. The bone marrow showed a total lack of fat and was made up wholly of myeloid tissue with comparatively few normal or nucleated red blood corpuscles, the megaloblasts predominated. Myelocytes occurred in groups with the characteristic large vesicular nucleus with a small amount of finely granular basic staining cytoplasm. The marrow of the diploë was markedly hyperplastic and had the same appearance of myeloid tissue found in the marrow of the long bones.

There are more cases of pernicious anemia reported in boys than girls, which agrees with the findings in adults. Hereditary factors probably play some part as it is fairly common to obtain a history of other cases in the family. In most cases, no causal factor of enough importance can be found to account for such a serious anemia. Even

* D'Espine, A., Rev. med. de la Suisse Rom., xxxviii (Aug., 1918), p. 461; abstr. J. A. M. A., lxxi (Oct. 26, 1918), p. 1444.

† Morse and Wohlbach, Am. Jour. Dis. Child., xiv (Oct., 1917), p. 4.

where intestinal parasites have been blamed as the initiators, there are many factors that would tend to discredit their playing anything but a secondary rôle in the initiation of a true primary anemia. It must be remembered that the younger the child, the more often will their blood react with a picture resembling a primary anemia for a short period, when only a secondary anemia is really present.

The bone marrow changes are the primary and essential changes found in the disease. The naked eye appearance of the bone marrow is uniformly the same, though the microscopic picture of the bone marrow may vary somewhat, depending on which type of cell predominates. There is always a megaloblastic increase, and as the condition is more acute, there is always an increase in the fetal type of cell. The rapid proliferation of the red blood series pushes out or takes the place of granular leukocytes or macrocytes. This is shown in varying degrees in the peripheral circulation. The destructive process that goes on there does not attack the granular leukocytes or the platelets, but apparently is only toxic or destructive to the red blood series, and the proliferation in the marrow is an attempt to keep pace with the destructive process going on outside of the blood-forming organ, the bone marrow, so that at any given time a careful study of the blood will give us an index of whether destructive or regenerative processes are predominant. The exact etiology of the condition is unknown. A hemolytic agent is undoubtedly the cause of the condition primarily. Malaria, syphilis and intestinal parasites have all been the supposed cause of the manufacturing of the toxin. It is only fair to suppose that the bone marrow is either peculiarly susceptible in these cases, or the toxin generated has a peculiar affinity for the red cells in special individuals. Pernicious anemia does not follow severe hemorrhages nor is it found following acute or chronic hemorrhagic conditions. In pernicious anemia, the essential feature of the disease is the vulnerability of red blood-cells for destruction in the liver, spleen and lymph glands. It does not necessarily indicate that these tissues take any part in this destruction, but rather that the red blood corpuscles themselves are more easily destroyed. The accumulation of iron in the liver, kidneys, and spleen is due to the abnormal amount of general blood destruction by the toxin and does not necessarily mean that the seat of the toxin is in these organs. It may be in the intestinal tract, as it undoubtedly is in bothriocephalic anemia. At autopsy certain characteristic findings are present. There is a general fatty degeneration in most of the organs. This degeneration, particularly in the heart, gives the characteristic "tiger lily" appearance. The liver and spleen are often slightly enlarged. In the spleen the splenic pulp is found encroached with red blood-cells, while the sinuses have fewer cells than normal. Changes in the brain and spinal cord are often found.

The blood picture is undoubtedly the most characteristic finding. The red cells usually vary between one and two millions, the hemoglobin is 40 per cent. or below, the white cells are diminished, usually

below 4000, the color index is 1. This is the only anemia in which a persistent color index above 1 is a constant finding. In making smears it is found that the blood spreads out very easily. There is a rapid separation between the corpuscles and the plasma. The average size of the red blood-cell is found larger than normal and the cells stain more easily. Alteration in the shape is very common. Polychromia of the megalocytes is common, and granular degeneration is frequently found. The nucleated cells are usually of the megaloblastic type, though normoblasts are more common in children than adults. There is great variation in the size of the megaloblasts and the degree of polychromasia and basophilia varies greatly. They are usually two to four times as large as the normal red blood-cells. With the leukopenia there is a relatively high proportion of lymphocytes. The proportion of eosinophiles is changed very little. The blood platelets are invariably diminished and larger than are usually found, often being half the size of a normal red blood-cell. In acute cases the total number of red cells often falls below one million. The lowest count recorded is that of Quincke of 143,000 red cells. In chronic cases, the count is usually over a million. During a remission the red cells often increase very rapidly and there is a drop in the color index but this seldom returns to normal though occasionally for short periods the color index may be as low as 0.7.

Symptoms.—There are no clinical symptoms which are invariably present. The exact date of the onset is difficult to ascertain. The patient at some definite time begins to complain of muscular weakness. There is often a peculiar discoloration or pigmentation of the skin which has a lemon yellow appearance. Breathlessness is a common symptom, due partly to the cardiac dilatation but mainly due to the diminished number of red blood-cells. There is usually a definite systolic murmur with a rather rapid weak pulse. There may be definite lack of appetite which may be very persistent and difficult to overcome. Outside the blood findings and coloration of the patient, with a steadily progressive history, there is nothing else necessarily characteristic of the disease. Nervous symptoms are lacking in most cases. The special senses are sometimes definitely affected. Retinal hemorrhages are not uncommon. The sense of taste undoubtedly has a great deal to do with the lack of appetite. Temperature is usually present for long periods and may run fairly high in acute exacerbations and subside to normal during intermissions.

Diagnosis.—The diagnosis depends upon the systematic and careful examination of the blood. The blood picture should be carefully studied in all cases in which there is pronounced weakness especially if connected with persistent gastric or intestinal disturbances, vomiting, diarrhea and sore tongue, if these cannot be otherwise explained. Chronic debility, temperature and dyspnea also indicate careful blood examination, if these symptoms cannot be explained. A blood picture with a definite leukopenia, with megaloblasts and normoblasts, and a high color index makes diagnosis certain.

The condition cannot be diagnosed from any one of these factors. It is the evaluation of the efficiency of the bone marrow that is most important and a careful analytic study of the blood will give us not only data for diagnosis but also show us the exact stage of the disease and assist in evaluating different measures used in relief of the condition.

In severe secondary anemia, the diagnosis is, at times, difficult, for in these cases the more the red blood-cells are reduced, the higher becomes the color index and an increasing number of large red corpuscles make their appearance in the blood. When the megaloblastic reserve is sharply drawn on, the megaloblasts turn megalocytes out into the circulation. The color index does not usually exceed 0.9 in secondary anemia. In taking the hemoglobin, there are many chances of incorrect reading. This is especially true of such scales as the Tallquist and even with the Sahli hemoglobinometer, unless the standard solution is accurate and kept checked up with a known solution of hemoglobin, errors as high as from 15 to 25 per cent. will constantly occur. This has been already brought out in the discussion of hemoglobin in Chapter LXXIV.

The cases reported in infants and young children have run comparatively acute courses. Where diagnosis of bothriocephalus latus can be made the outlook is much better than in any other type. Even in these cases, however, cures are not always obtained. The disease itself has a tendency to remissions during which patients though they may not be entirely well, may lead a fairly normal life.

Treatment.—In the treatment rest and diet hold very important places. It is essential that the patient should live as far as possible in the open air. The more they are treated as we would treat cases of tuberculosis, the better the results. They should be protected from damp and cold and kept in bed until their hemoglobin is at least 60 per cent. The amount of exercise and play they take should always be regulated. The diet is just as essential. A diet high in the factors that stimulate or aid bone marrow development should be given with as high a caloric value and as well balanced as possible. Since proteins have a definite effect on blood formation, and certain vegetables, such as spinach, also aid in blood regeneration, the red meats and vegetables should be given as liberally as possible. A high carbohydrate diet probably depresses the blood forming organs so that it might be better not to give too high a carbohydrate diet. The question of fruit, liquids and other foods must be regulated according to special indications. Rigorous care of the mouth and teeth should be insisted upon. Constipation and diarrhea must be treated symptomatically. Arsenic is the one main remedy. It is best given as Fowler's solution, starting with 1 m. a day until the limit of tolerance is reached. The permanent dose should be two-thirds of the dose that produces symptoms. Cacodylate of soda has been used by some with favorable reports. Salvarsan has also been given with varying results. There is usually a very marked reaction after giving an intravenous injection

of salvarsan or neosalvarsan. Iron has been used alone, or in combination with arsenic but iron is contraindicated rather than indicated in pernicious anemia as there is plenty of iron stored in the liver and it may act as an irritant. Red bone marrow has been given but apparently does not do much good. Transfusion of blood has been employed with many good results reported. There is no question that repeated transfusions have tided over many critical periods and have aided in the initiation of remissions. The indirect method with citrated blood is to be preferred to direct transfusion. In the last few years, splenectomy has become an important method of procedure and is strongly advocated by some workers, but the analyses of splenectomy would indicate that this procedure is not as definite as could be hoped. The mortality has been high and relief only temporary in the majority of cases.*

SECONDARY AND IDIOPATHIC APLASTIC ANEMIA

Secondary anemia may be caused by tumors encroaching upon the bone marrow. In such conditions the effect on the bone marrow may be much more extensive than the size of the tumor would suggest. Evidently in such cases there must be some toxic or irritating substance which affects the growth or activity of the normal blood forming tissue. Such conditions are found in hypernephroma. Not only is the bone marrow affected but the spleen will often take on active bone-forming functions and there will be marked reversion to the embryonic conditions. Early marrow cells, megaloblasts, microblasts, normoblasts and myelocytes will be found, often in great number, in the blood.

In 1918 Jack and Teacher† reported a case of metastatic tumor of the sternum involving several ribs and extending into the vetebral bodies in which the blood picture was that of aplastic anemia. There was no attempt by the bone marrow to regenerate. Gulland and Goodall‡ say that in such severe cases "aplasia appears to be due to the severity of the toxin so that regeneration never takes place." This may explain the aplasia, but on the other hand we know that the nutritional condition of the individual affects the power of the bone marrow to respond to normal as well as abnormal stimuli. This, as we have pointed out, is especially true in the bone marrow in chronic nutritional conditions of infants and children. The response to stimulation in such cases is very uncertain. In some cases the power to form red blood-cells alone is affected and in such cases the type of secondary anemia which we have mentioned will occur. In other cases the formation of granular leukocytes will be affected, or the formation of platelets may be primarily affected. If all three are affected, we get a typical picture of true aplasia; if the platelets alone are affected, we get the picture of purpura hemorrhagica.

* Pearce, R. M., Krumbhaar, E. P., and Frazier, C. H., "Spleen and Anemia," Philadelphia (1918).

† Glas. Med. Jour., lxxz (1918), p. 81.

‡ "The Blood," 2d ed. (1914), p. 176.

Aplasia is due to the defective functioning of the blood forming organs. This may be complete or incomplete. In complete aplasia the red bone marrow is replaced by a fatty, yellowish, gelatinous marrow. In extreme cases this marrow may almost be fluid. The blood picture will depend entirely upon what portion of the bone marrow is affected. Experimentally, this type of defective bone marrow functioning can be produced by benzol. Such an aplasia often occurs during benzol treatment in cases of leukemia. If the benzol is pushed too far one sees a rapid disappearance of practically all the formed elements of the blood. The same thing will be true at times, though perhaps not so rapidly, when leukemia cases are being treated by radium or the *x*-ray. Certain intestinal parasites such as the fish tape worm produce an aplastic condition of the bone marrow. We have mentioned the fact that in certain cases of chronic secondary anemia the bone marrow will often assume for long periods of time a lower level of production than normal. Usually in such cases the formation of red blood-cells is more affected than is the production of granular leukocytes or platelets. The megacaryocytes are apparently the most resistant. This is probably a good example of nature's admirable protective mechanism, because interference with the production of platelets is more difficult to compensate for if it is lowered to any great degree than interference with the other formed elements of the blood.

During severe infections we at times see a marked response of the blood forming organs early during the infection, shown by a high leukocyte count. This is followed by a drop in the leukocytes far below normal. At the same time the blood will show the usual diminution in the red blood-cells and hemoglobin. With this combination we get a variable period at times of a diminution in the platelets, though they do not, as a rule, drop to the point of producing spontaneous hemorrhage. One sees this occasionally in the spontaneous hemorrhages from the mucous membranes during convalescence following these severe infections. This type of diminished production of bone marrow is short-lived because, fortunately, in children the recuperative power is great; but if the convalescence is prolonged or protracted or if the infection becomes chronic, we may see a permanent aplastic condition, sometimes of a mild, sometimes of an extreme degree, appearing.

The same thing probably is true of the bone marrow of syphilitics, in whom, previous to acute infection, there is a definite lowered reaction, particularly in the bone marrow, due to the primary luetic infection. The picture of these cases may almost be summarized as Krumbhaar* has summarized the results of gas poisoning in a review of 62 cases. His summary is almost identical with that we have occasionally found in infants and children following toxic infection:

"1. Certain forms of gas poisoning cause, after the initial leukocytosis, a more or less extreme degree of leukopenia.

* Jour. Am. Med., lxxii (1919), p. 41.

"2. This usually persists even in the presence of bronchopneumonia, and is very probably an important contributing factor to the high mortality of severe cases.

"3. If the leukocyte count falls below 1000 per cubic millimeter 'myelocyte crisis' may bring about a partial amelioration, but in the two cases observed of this count, this did not serve to protect from a fatal outcome.

"4. Lessened blood formation is also indicated by the production of anemia without blast cell formation and diminution in the number of blood platelets. In the earlier stages the coagulation time is decreased and in the later stages of severe cases it is increased."

These cases are most often considered as marked secondary anemia and they probably had better be considered as such, though we have mentioned them in this connection to draw attention to the fact that interference in the production of bone marrow may be produced; in other words, that secondary aplastic anemia does occur. This is not to be interpreted that we think that this is the usual response following infection, but simply to call attention that it does occasionally occur.

Idiopathic aplastic anemia does not occur often in children. Smith,* in reporting a case of aplastic anemia in a child six years of age, mentions being able to find 64 cases in the literature up to December, 1918. He seems to assume that secondary cases should not be classed with aplastic, that is to say, cases due to infection, gas poisoning or drug poisoning. We see no reason for not considering these as secondary cases of partial aplastic anemia. By aplastic anemia is meant a condition in which there is interference in the formative power of the bone marrow or red blood-forming tissue throughout the body, as differentiated from cases of anemia in which aplastic periods may occur. In true secondary aplastic anemia and idiopathic anemia there is no blood destruction. They are purely the result of diminished or absent productive power in the blood-forming organs. In true aplastic anemia all formed elements of the blood, erythrocytes, leukocytes and platelets are diminished. There may be a relative granular or actual increase in the lymphocytes. There are certain other definite changes in the blood depending upon the reduction of the platelets. The coagulation time may not be markedly interfered with. It may be slightly prolonged but the retractility of the clot is definitely interfered with and bleeding time is prolonged, showing that not only cytozym obtained from the blood-forming organs, but also the thromboplastic substance obtained from the tissues, is diminished. Fragility of the corpuscles to hypotonic salt solution is markedly altered, showing a change at both ends, hemoglobin occurring earlier in some cells and later in others than occurs in normal erythrocytes. This is to be taken, when it is found to any extent, as a marked reaction in the bone marrow and may indicate their inability to produce new red blood-cells. The appearance of the red blood cells themselves is very little altered either in shape or in size. The red blood-cells are very much

* Am. Jour. Dis. Child., xvii (1919), p. 174.

diminished in number, often to less than one million. The color index is not reduced, nucleated cells are not found, stippling and polychromatophilia do not appear and reticulated cells are difficult to find. The white blood-cells, as stated, are reduced, and the eosinophiles practically disappear. The polymorphonuclears seen are often small and with only two or three nuclei. According to the Arneth formula there is "a left-handed shift." The mononuclear cells and transitional cells may be slightly increased. Myelocytes and myeloblasts are rare though they may at times occur. The platelets are distinctly reduced in number and when they fall below 50,000 per cubic millimeters spontaneous hemorrhage such as is found in purpura hemorrhagica usually appears.

These two conditions, however, are to be clearly differentiated. In purpura hemorrhagica (which will be discussed in full later) there is simply a depression in the platelets. The red blood-cells and granular leukocytes are not at first diminished and the bone marrow shows signs of regeneration of red blood-cells and granular leukocytes, so that abnormal forms of both these elements may be found, especially immediately after hemorrhage. After hemorrhage, as the condition continues, a marked secondary anemia implicating the red blood-cells and granular leukocytes of course may occur, but the bone marrow shows a hyperplasia rather than the typical findings of a fatty marrow in aplastic anemia. A positive diagnosis of true aplastic anemia is often impossible to make, during life at least, as conclusive proof of aplasia depends upon the pathological condition of the bone marrow. As pointed out by Smith, at times there is a marked deposit of hemosiderin found in the liver, spleen and other organs. The complete, or almost complete absence of the bone marrow is the best proof of aplastic anemia. In some cases of true aplastic anemia small islands of blood-forming tissue may be found, but so surrounded with fatty gelatinous tissue that from a practical standpoint they might just as well not have been present as they are not able to deliver cells to the circulation. The etiology of the condition is not known nor are there any very striking symptoms except those referable to the anemia itself. The onset is often gradual and the first thing that is noted is the pallor which is often quite marked, and the scleræ are very white. Mucous hemorrhages or subcutaneous hemorrhages, especially from the mouth, usually occur, though not until the condition is well advanced. In these cases often a secondary septic process may be engrafted on the aplastic anemia.

During the course of lymphatic leukemia we at times get a stage in which aplasia is marked especially towards the termination, and as Selling* has stated, is shown also in benzol poisoning. This often occurs during the treatment of lymphatic leukemia with benzol, though it may occur where benzol has not been used, during the course of *x*-ray or radium treatment.

* John Hopkins Bull., xvii and xxi.

There is another type of anemia which may be placed in this general group described by Baboniex and Tixier,* Minot,† and Kleinschmidt‡ in which there is an enlargement of the spleen, marked evidence of bone destruction and aplasia of the bone marrow. These cases clinically, except for the fact that the bone marrow, spleen and at times the liver are enlarged, resemble the type of aplasia which we have been describing. The blood picture, however, may show more signs of destruction and the spleen may be at times quite enlarged.

Minot,§ in discussing this group of cases says: "Is it not possible that at times, with or without hypertrophy of the spleen, its physiologic activity is altered so as to cause bone marrow depression? It is, however, to be noticed that in the conditions called idiopathic purpura hemorrhagica and aplastic anemia the spleen is very rarely palpable and never much enlarged . . . such odd types of blood disease serve to show how we can find almost any combination of factors involving blood destruction and formation and how we can find examples intermediate between the different more clear cut types of blood disease."

Within the past year we have had opportunity of studying such a case:

George A. (U. of C. Hospital, No. 6074), aged three and one-half years. His family history was essentially negative. There was one other child in the family, younger, who was in perfect health. The boy was born at full term by natural labor, weighing 7½ lb. His infancy was normal. He was breast fed for the first six months and then was put on a whole milk formula. He had had no serious gastro-intestinal disturbances. His only previous illness had been a slight attack of German measles at two years and an occasional attack of indigestion usually with slight diarrhea lasting for one or two days, but at no time had he been very sick. His present illness began about two months before he was seen by one of us. The only symptom which he had shown during these two months was a progressive weakness, which had apparently followed a slight cold. During the period that he had slight coryza his left lip and cheek were somewhat swollen, but this had gradually subsided. His weakness and pallor became increasingly apparent. His physical examination on entering the hospital showed a very pale child. There was no pigmentation though his skin had a yellowish tinge. His scleræ were very white. There was definite puffiness under the eyes and a few fresh ecchymoses about both knees. The superficial lymph nodes were enlarged so as to be palpable, most of them being about the size of a pea. His lungs were clear. His heart was somewhat dilated especially on the right. There was a typical hemic systolic murmur heard all over the cardiac area transmitted to the axilla and back. On any exertion there was marked dyspnea and slight cyanosis. The liver was slightly increased, though not palpable. The spleen extended 3 cm. below the costal margin and the nipple line. Its edges could be easily made out but it was not tender. Examination of the stools showed occult blood and during his stay in the hospital covering a period of eight weeks before his death he had hemorrhages from the gums, epistaxis, bleeding from the lips and hematuria. As his case became more hopeless the tendency to hemorrhage became more marked especially during the last two weeks of life, notwithstanding repeated transfusions. The examination of the blood was made daily. His hemoglobin on entrance was 26 per cent. and after three transfusions at 10-day intervals it rose to

* Arch. d. mal du coeur, vii (1914), p. 28.
† Arch. Int. Med., xix (1917), p. 1074.
‡ Jahrb. f. Kinderh., lxxxi (1915), p. 1.
§ Arch. Int. Med., xix (1917), p. 1074.

its highest point of 69 per cent. After each transfusion his blood showed a tendency to react less and less. The color index throughout was high, 1 or above, resembling that of pernicious anemia. The neutrophil count was low throughout. There was a slight relative increase of the lymphocytes. During the first part of the observation normoblasts and megaloblasts were found in the blood but after the first few weeks they disappeared. However, as they disappeared myelocytes appeared. Irregularities in the size, shape and staining reaction of the red cells were constantly present. The platelet count was always low. As stated, on entrance his hemogoblin was 26 per cent.; his red cell count, 1,284,000; color index, 1 per cent.; white cell count, 20,000; neutrophils, 13 per cent.; no eosinophils; one basophil; 25 per cent. small lymphocytes; 18 per cent. large lymphocytes; one endothelial cell; 41 per cent. fragmented cells; acromia was slight; polychromatophilia slight; no stippling; very slight poikilocytosis; seven megaloblasts and one normoblast to 100 cells. After the first transfusion his hemoglobin rose to 47 per cent., but his red count only rose to 1,780,000, giving an index of slightly over 1. His white count at this time was 8600, 22 per cent. neutrophils, 2 per cent. eosinophils, 23 per cent. small lymphocytes, 24 per cent. large lymphocytes, 4 per cent. endothelial cells, 21 per cent. fragmented cells, no achromia, slight polychromatophilia, anisocytosis very moderate. A few microcytes and macrocytes, slight poikilocytosis, two normoblasts, seven megaloblasts; platelets markedly decreased with a few large in size. After the second transfusion his hemoglobin rose to 65 per cent., red cells to 3,012,000, giving a color index slightly over 1. The white cells were 7900, neutrophils 16,000, eosinophils 1 per cent., no basophils, 32 per cent. small lymphocytes, 19 per cent. large lymphocytes, one endothelial cell, 29 per cent. fragmented cells, two 2 per cent. vacuolated cells, no achromia, slight polychromatophilia, slight anisocytosis, slight poikilocytosis, two megaloblasts, platelets remained decreased but normal in shape, two myeloblasts. This was the best blood picture he ever showed as regards hemoglobin and number of red cells. His hemoglobin and red cells gradually diminished. In all he received nine transfusions during the course of eight weeks. Before his seventh transfusion his hemoglobin was 31, his red cells 1,232,000, giving a color index of 1.29 per cent. His white cells were only 800; they had greatly diminished, with very slight oscillation, once going up to 11,000 but diminishing rather rapidly after exposure to *x*-ray and radium. After these exposures they fell to 3000 and then gradually to 1000 and, as stated, just before his seventh transfusion they were 800, with a neutrophil count of 10 per cent., no eosinophils, no basophils, 22 per cent. small lymphocytes, 40 per cent. large lymphocytes, 13 per cent. fragmented cells, 12 per cent. unclassified cells. These cells had been increasing in number, and they probably belonged to the pre-myelocyte group, as the myelocytes and myeloblasts at this time were always present, averaging 13 to 100 cells. His platelets had varied throughout the whole course from 52,000 when he first entered the hospital. The highest point they ever reached after transfusion was 97,000. They gradually fell, though just before death, after the ninth transfusion, they rose to 112,000. The lowest figure they ever reached was 40,000. During this latter period there was always a considerable number of large sized platelets. Throughout the course a few microcytes and macrocytes were usually to be found on searching carefully. At no time were there any bone marrow cells found. After the seventh transfusion he had a splenectomy. Following this he failed rapidly and on the day of his death his hemoglobin was only 11 per cent., red cells 750,000, with a color index of 1.79, white cells 900, endothelial cells 7 per cent., small lymphocytes 43 per cent., large lymphocytes 23 per cent., fragmented cells 7 per cent., vacuolated cells 1 per cent., unclassified 6 per cent. There was slight achromia and slight anisocytosis, very few microcytes, slight poikilocytosis, no normoblasts, 13 per cent. myelocytes and platelet count of 112,000, for a few days previous to this it had been 46,000. Just why his platelets increased at this time and all his other cells diminished is hard to say because he was oozing continuously. Ante-mortem this case was rather puzzling as generally the picture was that of an aplastic anemia though on account of not having had an opportunity of studying the blood earlier the fact that the spleen was enlarged and

that the glands generally were easily felt one could not be sure that it was not an aplastic phase of leukemia. Against being aplastic anemia was the presence of slightly high color index and the presence of abnormal cells. The examination of the spleen after splenectomy showed a very large spleen weighing 495 gm. There was quite marked myelogenous alteration microscopically, suggesting activity on the part of the spleen in building up white cell waste. There were likewise occasional red cells with mitotic figures. The autopsy was incomplete; the bone marrow of the tibia was examined. The marrow had almost entirely disappeared and showed a thin almost fibrinous hemorrhagic substance. The red cells were individually not like those of pernicious anemia though they contained a high percentage of hemoglobin and showed no pallor, only slight poikilocytosis and very slight anisocytosis. The red cells were found to be abundant but there was no evidence whatever of a regenerative activity. Evidence of regeneration of the cells of the series was more marked but there was less than the normal number of myelocytes and myeloblasts and strikingly less were found in the spleen. Even with this incomplete autopsy it is impossible to make an absolute diagnosis. It may be, as Minot suggests, that "there may be a group of acute idiopathic hemolytic anemias which terminate with aplasia."* This case showed evidence of blood destruction, enlargement of the spleen and aplasia, at least the evidence of a marked degenerative hemolytic condition of the bone marrow, which had been unable to deliver the normal amount of any of the blood cells, neither reds nor whites nore platelets. On the other hand, the enlargement of the spleen and the fact that there was a myelogenous activity, might suggest that this was merely one of those cases of terminal aplasia in the course of leukemia. The case is simply cited as one of those in which, without having had opportunity of a more complete autopsy, even with the findings in the spleen and bone marrow, it is almost impossible to classify such a blood condition.

IDIOPATHIC PURPURA HEMORRHAGICA

Minot has defined purpura hemorrhagica as "a condition in which we have bleeding from one or more mucous membranes often with purpuric skin lesions, associated with a diminution of blood platelets, a delayed bleeding time and a non-retractile, soft blood clot. The coagulation time is normal or slightly delayed, rarely much delayed." This type of aplasia of bone marrow is far more frequently met with in children than is aplastic anemia. It is often confused with hemophilia, and has been called peeudo-hemophilia. It may be acute, subacute or chronic. Minot believes that there are congenital and hereditary types of idopathic purpura hemorrhagica. The pathology of such a condition is one in which the bone marrow, for some reason unknown, is not able to produce platelets. The anemia that is usually found accompanying idiopathic purpura hemorrhagica is due to the repeated hemorrhages and is a simple secondary anemia which shows, following a hemorrhage, the same blood picture of regeneration as regards red blood cells and granular leukocytes that occurs following any ordinary hemorrhage. However, after repeated or continuous hemorrhages there is often a marked deficiency in the power of the bone marrow to produce red blood-cells and granular leukocytes. There is no sign of destruction or hemolysis. The red cells vary very little in shape, though variations in size are not infrequently found. The color index is usually low as it is following most hemorrhages. Polychromatophilia and stippling with occasional normoblasts are seen. Reticula-

* Oxford Med., ii, p. 607.

tion of red cells is increased and is the best indication of the functioning of the bone marrow. There is an increase in the granular leukocytes. The response of the bone marrow is apparently the same as following hemorrhage. If the hemorrhage is acute there is quite a marked response but if it is continuous and chronic there is a much less marked response from the bone marrow. Minot considers there is a tendency to a left-handed shift (Arneth). In other words, the older cells are fewer and the younger cells predominate, a further indication of bone marrow regeneration, which differs from the right-handed shift in pernicious anemia. The platelet count is markedly diminished and this is the most clear-cut finding and is an aid not only in diagnosis but also in differentiating it from a post-hemorrhagic anemia, in which the platelets are often markedly increased. When the platelets have diminished to 50,000 or 60,000, spontaneous hemorrhage from the mucous membranes, hematuria, epistaxis or hemoptosia usually occur. Petechiæ and ecchymoses are frequent. Duke* has studied the platelets in all types of purpura very extensively and has demonstrated their relationship with that of the increased bleeding time, which may be very markedly increased, and lowered prothrombin and thromboplastic conditions. Minot† reports autopsy findings on a boy of 14 with purpura hemorrhagica. He says the red marrow showed evidence of active regeneration of the red and white cell elements. The megacaryocytes were plentiful, perhaps slightly increased above normal numbers. This picture is similar to that found in experimental purpura hemorrhagica produced by injection of anti-platelet serum by Lee and Robertson.‡ The megacaryocytes showed slight alteration and no diminution in number and they conclude that the cause of the diminished platelets was due to their destruction in the circulation. The platelets are apparently formed in normal number or even in increased number but are constantly destroyed in the circulation. Minot thinks that "the congenital and acquired types of purpura hemorrhagica might well be compared to the congenital and acquired types of hemolytic jaundice, in the former the platelets being involved in a similar fashion as the erythrocytes are involved in the latter." Minot suggests three possibilities for this condition occurring:

1. There may be a destruction of platelets in the plasma.
2. There may be a specific toxic action to destroy megacaryocytes or bone marrow in general.
3. That the megacaryocytes are unable to allow platelets to be cut off from them in the normal fashion.

Whichever one of these might exist the blood picture would be the same. Minot considers this idiopathic purpura hemorrhagica "to be a chronic insufficiency of the blood platelets, or congenital hypoplasia of the marrow or insufficiency of the marrow with special involvement of the platelets."

* Arch. Int. Med., x (1912), p. 445.
† Arch. Int. Med., xix (1917), p. 1171.
‡ Jour. Med. Research, xxxiii (1916), p. 323.

Minot gives a classification of conditions in which the platelets are involved in some manner which occurs specially in children and young adults:

1. Pure aplastic anemia. Duration, weeks; always fatal.	Aplasia of all elements of the marrow; red cells especially involved.
2. Purpura hemorrhagica.	
A. Continuous, acute or chronic; duration few days to months or even years.	Involvement of platelets only due either to interference with their formation, to abnormally rapid destruction or a combination of factors; hyperplastic or normal appearing marrow occurs in some instances.
B. Intermittent or relapsing, duration of attack days or weeks. Number of attacks two or more, over period of months or years.	

Either *A.* or *B.* may terminate with aplasia or exhaustion of the marrow involving all its elements, or at any time appear as intermediate types. In type 2*A.* it is to be noted that platelets are always diminished below normal. With attacks of bleeding they become more diminished, or may throughout the course of the disease remain so low that purpuric symptoms are constantly present. In type 2*B.* the platelets are diminished below normal only with the attacks.

3. Intermediate type of bone marrow involvement usually called purpura hemorrhagica.	
This may be the end result of Type 2, or appear as the subacute or chronic form. Duration, weeks or more; usually over months or years; may be intermittent in the intensity of the involvement of the marrow elements.	Platelet elements of marrow involved with varying degrees of depression or aplasia of either or both the white and red cell elements of the marrow. Perhaps some platelet destruction also occurs.

That aplasia of various degrees occurs there is little question. It is important that aplastic conditions should be differentiated from conditions of secondary anemia with simply a temporary lowered threshold of efficiency. Certain hemorrhagic conditions are at times mistaken for purpura hemorrhagica. Secondary anemia conditions may at times be mistaken for aplasia though there is less danger of making such a mistake than in confusing purpura hemorrhagica with other hemorrhagic conditions.

Purpura hemorrhagica should be differentiated from drug purpuras, Henoch's purpura, purpura rheumatica and purpura simplex. In these conditions the blood platelets are not interfered with. Sometimes they may be normal in number, sometimes above the normal. The purpuras that occur as secondary manifestations in other diseases are never of the type of true purpura hemorrhagica. In true purpura hemorrhagica joint symptoms are very rare. A careful study of the platelets will make a positive differential diagnosis always possible.

Hemophilia is probably the condition with which, according to Minot, there is at times more confusion. In true hemophilia there is usually if not always a family history of bleeding. The number of

platelets may not be diminished in hemophilia, though the coagulation time and prothrombin time of the blood is always delayed; while it will be remembered that in true purpura hemorrhagica coagulation time is not markedly interfered with but bleeding time is much prolonged. The blood clot in the two conditions differs. In purpura hemorrhagica it does not retract normally, while in hemophilia it does.

Minot states positively that true hemophilia does not occur in the female, though usually the possibility of this occurrence in proportion of about 1 to 13 in families congenitally known to be hemophiliac has been reported. This occurs in the clinical review of hemophilia by Bulloch and Fildes.*

Minot feels that the females of such families belong to the chronic type of purpura hemorrhagica. In the few cases of true hemophiliac families that we have had an opportunity of studying, the blood resembled more closely that of true hemophilia than purpura hemorrhagica. At the present time we would feel that this is still a question open for careful investigation. At any rate there could be little doubt that there are probably more cases of chronic purpura hemorrhagica than of hemophilia. In any such case a careful study of the factors entering into coagulation time, bleeding time, platelet count, re-calcifying time, prothrombin content and ability of the clot to retract are all to be estimated.

It is at times almost impossible to differentiate true aplastic anemia from the aplastic phase of leukemia. The fundamental pathology of the two conditions is entirely different. In leukemia the reduction in the formed elements of the marrow is due to the fact that these cells have been crowded out by the growth of the lymphocytic cells or the myelocyte cells. The marrow is really infiltrated by tumor cells but what marrow is left is still capable of producing the normal formed elements. The symptomatology and blood picture during the aplastic stage of leukemia may be the same as that of true aplastic anemia though usually signs of bone marrow degeneration in the type of cells present, the reticulation, the nucleated red cells and the abnormal staining of the cells, and also the change in size and shape, would point to an aplastic phase of leukemia. Whereas, in aplastic anemia there is less change in the type of cells seen and the marrow shows an absence of any type of regeneration, the marrow being replaced by a fatty tissue rather than being crowded out by tumor cells as in leukemia.

The type of lymphocytes may also help in the differentiation. In lymphatic leukemia there tends to be a variation in the size of the lymphocytes. Large lymphocytes with pallid nuclei or cells with lobulated nuclei may be made out. These are all suggestive of lymphatic leukemia. Of course if the lymphatic glands are found enlarged this is another suggestive point and the percentage of lymphocytes in leukemia is usually higher than that found in aplastic anemia.

* "Monograph on 200 Hemophiliac Families." Eugenic Lab. Memoirs, Univ. of London, vii (1911), p. 169.

The differentiation of aplastic conditions from conditions in which bone marrow has been invaded by tumor cells has already been mentioned. In these cases atypical cells will be found in the circulation and may aid in the diagnosis.

In childhood differentiation between true aplastic anemia and pernicious anemia rarely arises, as pernicious anemia is so rare. The color index in pernicious anemia tends to remain high, while in aplastic anemia it is usually low. If abnormal cells are present it would point to pernicious anemia rather than aplastic.

At times differential diagnosis between aplastic anemia and splenic anemia is difficult. The spleen, however, in splenic anemia is usually enlarged and the liver is also usually enlarged, in some types very markedly so, but the blood picture may be the same in both conditions, showing a diminution in all the formed elements with no signs of destruction. At times, however, in true purpura hemorrhagica the spleen may be found slightly enlarged so that a differential diagnosis during life may be impossible. As has been stated, the final diagnosis of aplastic anemia always rests on the pathological findings of the bone marrow and blood forming organs.

Treatment.—There is no specific treatment. The cases are always fatal. The only treatment which is of any value is (1) supportive and general hygienic and dietetic measures, and (2) transfusion which may prolong life for a short period. *X*-ray or radium treatment if given in small, stimulating doses might be of some value, though this is doubtful.

BANTI'S DISEASE*

This condition is characterized by a very marked enlargement of the spleen, and in later stages by enlargement of the liver with jaundice and cirrhosis. The blood picture is little changed, except for moderate leukopenia. The cause of the disease is unknown, though many theories have been advanced as to the etiology. The disease runs a very chronic course extending over years rather than months, unless splenectomy is performed early in the disease.

Historical.—Banti first in 1883 described a condition in which cirrhosis with an enlarged spleen was noted. In 1894 he further showed that ascites was commonly found in the latter stages and suggests, through clinical and experimental evidence, that the primary cause was in the spleen, and he first suggested for this reason the removal of the spleen.

Etiology.—The etiological factor is still in debate, the main difference of opinion being as to whether Banti's disease is due to a specific cause or is merely a fairly constant symptom-complex. Banti himself attempted to demonstrate microörganisms in the blood and viscera but he failed, as have nearly all other investigators, in producing the disease in experimental animals. He felt certain, however, that the spleen was primarily involved. He attempted to demon-

* Banti, G., La splenomeglia con cirrosi spatica sperimentale, xlviii (1898). p. 407.

strate that the erythrocytes in their passage through the spleen are so acted upon by some unknown substance as to become more susceptible to hemolysis, and maintained that free hemoglobin can be demonstrated in the splenic veins.

Pearce* suggested that the fact that the spleen is involved earlier than the liver would point to a hematogenous rather than a enterogenous toxin. They however state that there is no question that various conditions, such as atypical cirrhosis of the liver with early prominence of splenic signs, syphilis, or primary endophlebitis or thrombosis of the splenic or portal vein can produce a picture which cannot be distinguished from that of Banti's disease. Yates, Bunting and Kristjanson† have attributed the disease to diphtheroid organisms found in the spleen though they were unable to reproduce the condition. Kristjanson,‡ however, in 1919 isolated a cocoid organism from a case of Banti's disease and was able to reproduce it by intravenous injection in the dog. This is, as far as we know, the only successful animal experiment, and has not been confirmed by other investigators. Gibson§ has reported finding of streptothrix in the spleen in certain cases which resemble Banti's disease. Graham‖ states that Banti's disease is due to an enlarged spleen which develops toxin that produces the disease. It is certainly a fact that if the spleen is removed early before secondary changes have occurred in the liver that complete cure, or at least what amounts to a cure, is very often accomplished. Whartin¶ insists that an infectious thrombophlebitis of the splenic or portal vein is the essential feature of the symptom-complex, whereas the upholders of the separate entity theory claim that such changes are secondary to the changes in the spleen, or may be absent altogether in typical cases of Banti's disease.

Pathology.—The spleen is enormously enlarged; the capsule is thickened and there is a great increase of the fibrous tissue. The malpighian bodies are atrophied, the cells in the pulp are scanty, though the lymphocytes predominate. There is a good deal of pigment in the cells or lying free in the pulp. The liver also shows a marked increase in fibrous tissue which spreads throughout the liver in such a way that the lobular structure is destroyed and many lobules are in this way cut off. The fibrous tissue is infiltrated with leukocytes. Pigment can be found in the endothelial cells and the capillaries but not frequently in the liver cells. There is marked activity of the red bone marrow which extends into the shaft of the long bones. The normoblasts are somewhat increased and there may be a slight increase of myelocytes also. There is little or no sign of leukocytic activity, the

* Pearce, R. W., Krumbhaar, E. P., and Frazier, C. H., "The Spleen and Anemias" (1918), Lippincott, Phila.

† Jour. Amer. Med. Assoc., lxiii (1914), p. 2225.

‡ Wisconsin Med. Jour., xviii (1919), p. 125.

§ Gibson, A., Proc. Roy. Soc. Med., section vii (1914), p. 7.

‖ Graham, E., "Dis. of Child. Textbook" (1916), Macmillan.

¶ Whartin, G., Splenectomy and Thrombophlebitis, Internat. Clinics, iv (1910), 189; Am. Med. Sc. (1904), p. 119.

lymphocytes, however, predominate. The giant cells are scanty and degenerated. Iron pigment is also found in the leukocytes and endothelial cells of the bone marrow. The kidneys also show fibrosis with very little other change.

Symptoms.—The condition starts in childhood but does not make itself felt often until somewhere between 20 and 30. The disease has occurred in more than one member of the family but it is probably not hereditary in character. The causal factors are not understood. There are, however, certain fairly definite periods in the disease which may be described as stages: The first stage is represented by an enlarged spleen. This is usually discovered by accident, though occasionally there may have been a perisplenitis. Children may complain of lassitude and weakness and at times there is an unexplainable leukopenia with no changes in the red blood cells. This stage may cover several years though our knowledge concerning this stage is indefinite. The condition of Banti's disease is usually recognized during the second stage, when the first symptom may be that of hemorrhage; most often bleeding is from the esophageal varices and gastric veins, which have been found markedly dilated even in early operations for removal of the spleen. This hemorrhagic condition is usually associated with more or less prominent gastro-intestinal symptoms. The gastro-intestinal symptoms in children are often the ones which call for attention, and upon examination the enlarged spleen and a secondary anemia are found. During the second stage, the liver is apparently not involved, though it may be slightly enlarged. The third stage is marked by cirrhosis of the liver, and ascites is first noticed. The spleen during this stage often diminishes in size. The symptoms of hemorrhage and gastro-intestinal disturbance which appeared during the second stage are now increased in frequency and severity. The anemia usually parallels this development.

Blood Changes.—As stated, leukopenia is the first prominent blood change and occurs during the first stage. During the second stage, the red blood cells are found diminishing; the counts of the red blood cells vary between two and three million. Apparently the hemoglobin is more affected than are the number of red blood cells, and may reach the low figure of 30 and 40 per cent. This is not so low as the percentage found in aplastic anemia; the blood picture resembles more nearly that of chlorosis. The color index is much below 1. Often change in the size of the red blood cells is found. Normoblasts are rarely found. Megaloblasts may appear. Granular degeneration and polychromasia may be marked features, though in some cases the reduction in the hemoglobin is the most marked feature. The increase in urobilin is the most constant and characteristic sign of blood destruction. Fragility may be slightly increased but is usually normal. The white cells are never increased in number unless there is a secondary acute infection or after hemorrhage and then only for a short period. The diminution in the number of white blood cells is one of the earliest and constant features of the

disease. At times the white blood cell count is found under a thousand per centimeter and the count may even drop lower. There is usually a relative increase in the polymorphonuclear cells. This is only relative because the lymphocytes are mainly affected in the decrease, but actually all the cells are affected. The eosinophils are most markedly affected and tend to disappear. There is decided chronicity in all these stages. The changes occur very slowly, the same blood picture remaining for months or even years. This accounts for the fact that most cases begin in childhood and do not terminate until young adult life. This, in a measure, complicates the diagnosis.

Diagnosis and Differential Diagnosis.—It is at times impossible to differentiate the condition from the splenomegalies found in syphilis or malarial infections. The Wassermann in one instance, and careful and repeated examinations for the plasmodia in the other, are the only way in which differential diagnosis is made possible. The history of the condition also should aid one in making a diagnosis. At times during chronic infections there may be periods when the diagnosis between Banti's disease and the splenic and liver enlargements in cases of chronic infection may be rather difficult to separate. However, the history of the cases is usually suggestive, and with chronic infections, leukocytosis is usually found present. Amyloid enlargement of spleen and liver has been found especially in children suffering from chronic infections (osteomyelitis) which may resemble somewhat Banti's disease, but the history and their physical findings usually make easy the separation of the two conditions. Early in the disease with simple splenic enlargement and leukopenia, it is often impossible to make a positive diagnosis. During this early stage the condition differs entirely from the splenic anemia of infants in which there is always a leukocytosis and usually a definite history of malnutrition and rickets. The splenic enlargements due to intestinal parasites can be excluded only after repeated and careful examination of the stools. In parasitic infections, the eosinophils are increased rather than decreased as is the rule in Banti's disease. The course of the disease is very much more rapid in infections from parasites than in Banti's disease. It is difficult often to distinguish Banti's disease from Gaucher's splenomegaly. In Banti's disease, especially in the second and third stages, the development is more rapid than in Gaucher's disease. In Banti's disease, the anemia is more pronounced, and tendencies to hemorrhages are more pronounced, and in the third stage, jaundice and ascites are fairly characteristic of Banti's disease but are rarely found in Gaucher's disease. In the latter there is a tendency for the liver, as well as the spleen, to increase in size. The discoloration of the skin and the peculiar wedge-shaped thickening of the conjunctiva, seen on both sides of the canthus, make the differential diagnosis fairly simple though undoubtedly many reported cases have been confused and only positively determined on examination of the spleen. Further, Gaucher's disease often appears in several members of the same family.

Congenital hemolytic jaundice shows increased fragility of the red blood cells, and the increased reticulation and finding of urobilin in the stools should aid in making a differential diagnosis, as well as the presence of acholuric jaundice. Hemolytic jaundice is so rare in infants and children and the process so acute and the signs of acute blood destruction so prominent that there should be little trouble in differentiating the two conditions.

Leukemia and Hodgkin's disease present little reason for difficulty, though at times probably the lack of careful investigation of the blood and the fact that in leukemia periods of aplasia occur with leukopenia have produced difficulties and mistakes in making a correct diagnosis.

The fact that Hanot's cirrhosis occurs during childhood may create confusion. However, the fact that in Hanot's cirrhosis the liver is primarily involved, and the fact that there is fever and leukocytosis, should remove any cause for confusing these conditions.

Prognosis.—The disease is characterized by prolonged remissions followed by sudden and acute exacerbations, after which the condition is permanently worse than before. The history is that of gradual progression over years during which the patient is a semi-invalid. Fatal terminations usually occur after sudden hemorrhages, which are more frequent late than early in the course of the disease but may occur any time. Secondary infections are often the cause of a quick decline. Prognosis is always dubious.

Treatment.—Removal of the spleen early in the disease is the only logical treatment. The result of operations during late years has given a very low mortality—since 1910 as low as 11.1 per cent. Where deaths have been reported they have usually been in cases where the operation was done in the third stage, during which other complications, such as cardiorenal and thrombosis of the portal vein, have been the direct cause of failure rather than splenectomy itself. Splenectomy should never be done during a period of exacerbation. If the spleen is removed during the first stage, a practical cure can be expected or, at least, the prolongation of life and well-being of the patient is such that he can be considered as practically cured.

Even when the operation is done during the third stage in the presence of ascites and cirrhoses, splenectomy, if combined with omentopexy, may give a prolongation of life and freedom from symptoms for several years. Lozio* has reported such a case lately. When for any reason splenectomy cannot be performed or is not permitted, *x*-ray treatment or radium treatment would seem to offer results that might favorably affect the course of the disease, though it is doubtful whether cures such as are obtained by splenectomy can be hoped for by these means. There is no question that both the *x*-ray and radium will at times bring the spleen back to normal size and the blood picture will also return to its normal limits. The effect of radium on various splenomegalies seems to be greater and more lasting than is the result

* Lozio, L., Splenectomie et Omentopexi pour splenomegalic, Primitive Presse Med., xxviii (1919), p. 415.

of x-ray treatment. In the later stages where only palliative measures are indicated, restricted activities and a nourishing diet, combined with arsenic given in increasing doses up to the point of toleration (Fowler's solution) and continued over a long period may give moderate relief. The injection of salvarsan or neo-salvarsan may be tried as it has been in almost all splenomegalies, but we would not recommend its use. Throughout the whole course of the disease care for the general health is of the utmost importance. In the early stages a definite routine and diet should be laid out to cover a long period of years. Transfusion at the time of acute hemorrhages is of undoubted value and in late stages it may have definite effect in stopping exacerbation and favoring an earlier remission than might otherwise be expected. As in all anemias transfusion is a stop-gap procedure and may always be counted upon to better the condition, at least temporarily.

GAUCHER'S DISEASE

Historical.—In 1882 Gaucher reported a woman 32 years of age who had had a splenic enlargement since 7 years of age. Her symptoms during the 25 years in which she lived in this condition were repeated epistaxis, bleeding from the gums, a progressively enlarging liver and spleen. She died from intercurrent pulmonary tuberculosis. At autopsy her spleen weighed 4770 gm. (normal 120 gm.), the liver was moderately enlarged, the lymph nodes were apparently normal. Gaucher considered this case to be a primary epithelioma of the spleen. Most writers in describing cases of splenomegaly of this general type have given it the name of splenohepatomegaly of Gaucher. It has been variously described as endothelioma of the spleen; some have considered that the large cells have arisen from the endothelium of the hematopoietic system. Others consider that there is a hyperplasia of the spleen with the development of characteristic endothelial cells from the reticulum and a marked overgrowth of dense connective tissue. It has been described as a systemic disease of the lymphatic system which primarily affects the spleen, then the lymph nodes, liver and bone marrow. By others, the enlarged spleen is considered as a new growth.

Etiology.—The disease is undoubtedly congenital but not hereditary. In most of the series reported, two or more members of the same family have been affected. In no series of children has either of the parents suffered from this disease, nor has it been transmitted from any adult to a child, as far as the reported cases go. There have been 17 authentic families reported in the literature, with a total of 23 cases. The disease is more frequently found in females than in males, 15 out of 18 cases. Splenic enlargement has been reported as early as the second month of life.* However, the average age at which the splenic enlargement was first noted was between three and one-half and four years.

* Niemann, Ein unbekanntes Bild der Kinder, Jahrb. f. Kinderh., lxxix (1914), p. 1.

Pathology.—The findings in the spleen have been almost identical in all autopsied cases. The spleen is very much enlarged; the surface of the spleen is white, smooth, with the fibrous coat considerably thickened and numerous adhesions on the external surface. The normal form of the spleen is usually retained. The spleen is firm and the cut surface has a fairly normal appearance with the exception of firm pyramidal shaped areas of a whitish yellow color. The microscopical examination of the spleen is very characteristic. The normal appearing splenic tissue is marked by large irregular spaces which are filled with large cells which vary in shape, being either round or oval; their nuclei vary in size and shape. These cells have undoubtedly sprung from the endothelial lining of the pulp spaces of the normal spleen. The spaces often communicate with each other. Giant cells are also found. The normal pulp cells have entirely disappeared. Areas of increased connective tissue are found in which there are practically no cells, except the small round cells which have infiltrated these dense whitish areas of connective tissue. In other areas, there seems to be an increase in the capillaries. The capsule, with its interlacing trabeculæ, is much thickened. The malpighian bodies show little or no change.

The liver is firm and smooth and much enlarged. The capsule is thickened as well as all the connective tissue throughout the liver. Old and new infarcts may be seen and islands of glistening, whitish tissue. There is considerable pigment, especially in the capillaries. Large endothelial cells, similar to those seen in the pulp spaces of the spleen, are found in the interlobular spaces. The liver cells as well as the bile ducts are apparently normal. Lymph-nodes are enlarged and there are many endothelial cells and considerable pigment. On section, the nodes appear to have a deep red center with a pale periphery and are often quite soft. The bone marrow usually has the same dark pigment and the same large endothelial cells which are present in the spleen, liver and lymph-nodes. It is the characteristic cell of the splenohepatomegaly of Gaucher.

Symptomatology.—The gradual progressive enlargement of the spleen is characteristic of this condition and is usually the first sign noted. The spleen often attains a very large size. Due to its slow progress, there is no tenderness and very little inconvenience to the patient and it may be years before any secondary symptoms arise. The condition is very often discovered accidentally. The average weight of the spleen is over 1000 gm. and may weigh as much as 6000 gm. The normal weight of the spleen is from 120 to 150 gm. In one case reported by Collier, the spleen weighed 4 lb. 2 oz. whereas the child weighed only 23 lb. Bovaird* gives an example of a child weighing 78 lb. with a spleen weighing 12½ lb. The normal relation of the spleen to the body weight is as one to 400. In Collier's case it was as 1 to 5 and in Bovaird's 1 to 6.

* Am. Jour. Med. Sc., cxx (1900), p. 377.

The liver is usually enlarged but not to the same extent as the spleen. The hepatic enlargement may not occur until the spleen has reached considerable size. In some cases, the liver at autopsy has been found only slightly enlarged, or as large sometimes as the spleen. The splenic enlargement is always primary and the hepatic secondary. The lymph-nodes are rarely enlarged though there is definite increase with the characteristic endothelial cells. The blood picture is that of a mild anemia and is not a severe symptom until late in the disease and then is often due to hemorrhage. The size and shape of the cells are normal. The number may be as low as two and a half million. The white cells are usually diminished so that a leukopenia, in a case of enlarged spleen with little or no change in the red blood cells, is a very suggestive blood picture of this condition early in the disease. The hemoglobin is usually diminished more than is the number of red blood cells and in this point resembles the condition found in mild chlorosis. The differential count, however, remains within normal limits. At times there may be a slight eosinophilia and myelocytes are occasionally found. Pigmentation, especially around the eyes, face and neck, is usually present at some stage and is of a yellowish brown color. Wedge-shaped pigmentation of the conjunctiva has been described by Brill and Bendlebaum.* Hemorrhages may be persistent over a long period. Epistaxis and bleeding from the gums are the more usual forms of bleeding.

As the spleen and liver become large, there is usually abdominal pain. This may be simply a sensation of fullness and discomfort rather than actual pain. The children usually complain of fatigue and are subject to shortness of breath after slight exertion. As the anemia progresses, loss of appetite, emaciation, dyspnea and general weakness increase. There is usually no ascites nor jaundice. The condition progresses slowly in older patients. In infants, however, the progress may be quite rapid. In the case of the youngest child described by Niemann† the first symptoms appeared at two months and death occurred at 17 months, giving a duration of 15 months. In the two cases in infants reported by Knox‡ one died at the age of 11 months, the other at 15 months. In neither of these cases is the exact duration known. In both cases, however, there had been apparently a very early beginning as Knox notes that neither child had ever thrived. Both cases were followed for a duration of six months. The chart taken from Knox's admirable report to which have been added the two cases reported in his text, of 18 cases is given here.

In most cases some intercurrent infection causes the termination. In infancy and early childhood, the process ends much more rapidly than in adult cases where the duration is counted in years rather

* Am. Jour. Med. Sc. (June, 1909 and Dec., 1913).

† Niemann, Ein unbekanntes Bild der Kinder, Jahrb. f. Kinderh., lxxix (1914), p. 1.

‡ Knox, J. H., Mason et al, Johns Hopkins Hosp. Bull., xxvii, No. 299 (Jan., 1916).

than months. In adults the average duration is given as 19.3 years, except in those cases where death has been due to splenectomy. Neither syphilis nor tuberculosis play any part in the etiology of the disease. The Wassermann reaction has not been reported positive in but one of the authentic cases, that of Niemann.

In the study made by Wahl and Richardson* they found that the lipin content of the liver and spleen is markedly increased and that the normal relationship between the lipins is altered. The lipoids, lecithin and cholesterol, are markedly increased, while the fixed fats were reduced. Wahl and Richardson claim that the lipoid substances appear within the cytoplasm of the tissue cells, making the large pale cells distinctive of this disease. This derangement is related to a primary disturbance of fat metabolism, and the hematopoietic organs are only involved secondarily. These large pale cells occur in other conditions than Gaucher's disease and are, therefore, not entirely specific. They have been described in chronic granulation tissue, in chronic pyometria and pyosalpingitis. They have also been described in diabetic lipoidemia, and lately in connection with deficiency diseases in the bone marrow of cases resembling experimental scurvy. This is very suggestive, especially in relation to the two cases reported by Knox† which might fall into the acute deficiency conditions though there was nothing resembling scurvy.

Early diagnosis is very difficult, due to the lack of symptoms. The early suggestive symptoms are only present when the disease is fairly well developed, and are the primary enlargement of the spleen with a blood examination which shows but a light grade of anemia. The red blood cells are rarely affected early, even in number. The white blood cells may be slightly increased though there is more often a persistent leukopenia, but the differential count is within normal limits, so that leukemia, which might be suggested from the large spleen, may be easily excluded. The pigmentation, a brownish-yellow discoloration of the skin, is especially characteristic of the disease particularly if it is connected with conjunctival thickening with pigmentation. There is no edema, ascites, or icterus associated with enlarged liver. The frequent occurrence of the disease in more than one member of the family and its predilection for females, 15 out of the 18 reported cases where sex is noted being females, are also characteristic. The abdomen is usually very prominent but without any feeling of discomfort. At times there is a tendency to bleeding from the gums; epistaxis and petechiæ are not uncommon during exacerbations. During the long intermissions there may be no symptoms. The lymph-nodes are usually not enlarged. Altogether these symptoms make a complex by which it is fairly easy to differentiate Gaucher's disease from other conditions in which there is enlargement of the spleen. Splenic anemia, or von Jaksch's disease, may cause some confusion. The fact that in both

* Arch. Int. Med., xvii (Feb., 1916), pp. 238–259.

† Knox, J. H., Mason et al., Johns Hopkins Hosp. Bull., xxvii, No. 299 (Jan., 1916).

SUMMARY OF CASES

No.	Author and reference	Sex	Age at death	Age at onset	Chief symptoms	Physical signs			
						Spleen	Liver	Lymph glands	Color of skin
1	Gaucher: Thêse de Paris (1882).	F	30	7	Never robust; epistaxis, irregular menses, enlargement of abdomen. In last months, bleeding from gums, abdominal pain, edema of feet, fever.	51×25 cm. (by palpation). Weight, 4700 gm.	Extends to umbilicus. Weight, 3500 gm.	Enlarged slightly.	Leaden hue.
2	Collier: Tr. Path. Soc. London, xlvi (1895), p. 148.	F	6	2	Never robust; enlargement of abdomen, epistaxis, emaciation, subnormal temperature.	Weight, 2070 gm.	.....	Not palpable, mesenteric glands large.	
3	Picou and Raymond: Arch. de méd. exper. et d'anat. path., viii (1896), p. 168.	F	32	4	Abdominal pain, from fourth year, menorrhagia, bleeding from gums, edema of ankles, fever, loss of weight, enlargement of abdomen.	"Filled abdomen."	Three fingerbreadths below costal margin.	Enlarged at hilus of spleen.	Slight jaundice.
4	Bovaird: Am. Jour. Med. Sc., n. s., cxx (1900), p. 377.	F	13	3	Increasing enlargement of abdomen, shortness of breath.	Weight, 6250 gm.	Not enlarged.	Enlarged slightly.	Brown pigmentation, marked on face.
5	Brill, Mandelbaum and Libman: Proc. New York Path. Soc., iv (1904), p. 143; Am. Jour. Med. Sc., n. s., cxxix (1905), p. 491.	M	30	14	Sweating, epistaxis, enlarged spleen, pain in splenic region and in legs, petechial hemorrhages, dyspnea.	Weight, 5280 gm.	Weight, 4800 gm.	Enlarged in thorax and abdomen.	Brown pigmentation.
6	Schlagenhaufer: Virchows Arch. f. path. Anat., clxxxvii (1907), p. 125.	F	43	5	Enlargement of abdomen, edema of feet, bleeding from gums, epistaxis, increasing weakness, pain over liver.	31 × 20 × 12 cm. Weight, 3510 gm.	Weight, 3000 gm.	Enlarged.	Brown pigmentation.
7	Von Herzel: Wien. klin. Wchnschr., xx (1907), p. 123.	F	37	31	Epistaxis, during childhood. At 31 years, abdominal pain, vomiting, enlargement of abdomen. Later, chills and sweating.	32 × 16 × 12 cm. Weight, 3000 gm.	Extends a "handbreadth" below costal margin.	Enlarged slightly.	
8	Marchand: München. Med. Wchnschr., liv (1907), p. 1102; also Resel: Beitr. z. path. Anat. u. z. allg. Path., xlvi (1909),p. 241.	F	44	24	Pain in abdomen at 24 years. At 35 years, great weakness, myomatous uterus, ovarian tumor. Later, increased weakness, cachexia, hemorrhages in skin.	41 × 15 cm. Weight, 2720 gm.	24 × 26 cm. Extends 3 fingerbreadths below costal margin.	Enlarged.	Brown pigmentation.

9	Brill, Mandelbaum and Libman: Am. Jour. Med. Sc., n. s., cxxxvii (1909), p. 849.	F	42	21	At 21 years noticed abdominal tumor, sweating, hemorrhages of the skin, anemia, emaciation, epistaxis, bleeding from gums and bowel, dyspnea.	45 × 25 × 13 cm. Weight, 8100 gm.	35 × 30 × 12 cm. Weight, 3900 gm.	Enlarged slightly.	Brown pigmentation.
10	de Josselin de Jong u. van Heukelom: Beitr. z. path. Anat. u. z. allg. Path., xlviii (1910), p. 598.	F	12	7½	Enlargement of abdomen, weakness, bleeding from gums, attacks of syncope, vomiting.	Reaches to symphysis pubis.	Extends 2 finger-breadths below costal margin.	Not enlarged.	Yellowish-brown pigmentation.
11	Mandelbaum: Jour. Exper. Med., xvi (1912), p. 797.	M	4½	3	Enlargement of abdomen, slight abdominal pain, epistaxis, increasing languor.	18 × 9.5 × 5 cm. Weight, 490 gm.	Extends 3 finger-breadths below costal margin.	Much enlarged.	Yellowish pigmentation of face.
12	Wilson: Surg., Gynec. and Obst., xvi (1913), p. 240.	F	27	12	Frequent digestive disturbance, anemia, abdominal pain, edema.	Weight, 5280 gm.	Extends 3 in. below costal margin.	.....	Slight "jaundice."
13	Downes: Med. Rec., lxxxiii (1913), p. 697.	F	28	13	Enlargement of abdomen, loss of appetite, headache, emaciation, dyspnea.	35×13.5×6.5 cm. Weight, 1813 gm.	Extends 1 in. below costal margin.	Not enlarged.	Pigmentation of face.
14	Niemann: Jahrb. f. Kinderh., lxxvix, (1914), pp. 1–10.	F	17 mo.	2 mo.	Never thrived; indigestion, pallor, enlargement of abdomen, edema of eyelids and feet, low irregular fever.	Extends below level of navel.	Extends to 1 cm. above ant. sup. spine.	Enlarged slightly.	Pale-brown pigmentation.
15	Erdman and Moorhead: Am. Jour. Med. Sc., n. s., cxlvii (1914), p. 213.	F	3⅓	14 mo.	Healthy infant, large spleen noted at 14 months. From this time nervous indigestion.	Extends to level of umbilicus.	Extends 2 finger-breadths below costal margin.	Inguinal glands enlarged.	Pale; no pigmentation.
16	Herrman, Roth and Bernstein: Arch. Pediat., xxxi (1914), p. 340.	M	14	4	Large spleen noted at 4 years, abdominal pain, epistaxis, hematemesis, bleeding from gums, asthenia.	27 × 13 × 10 cm. Weight, 1320 gm.	Extends 5 cm. below costal margin.	But little enlarged.	Pale; brown pigmentation of face.
17	Knox, Wahl and Schmeisser: Johns Hop. Hos. Bull., xxvii, No. 299 (Jan., 1916).	F	11 Mo.	?	Never thrived; enlarged abdomen.	4½ in. below costal margin to level of umbilicus. Weight, 86 gm. 13 × 5 × 4 cm.	2½ in. below costal margin. Weight, 415 gm.	Enlarged slightly.	Brownish pigmentation.
18	Knox, Wahl and Schmeisser: Johns Hop. Hos. Bull., xxvii, No. 299 (Jan., 1916).	F	20 mo.	Before 5 mo.	Weak and emaciated; prominent abdomen.	2½ in. below costal margin. Weight, 100 gm. 10×6×3.5 cm.	2½ in. below costal margin. Weight, 420 gm. 28×10×4.5 cm.	Enlarged slightly.	Grayish yellow.

SUMMARY OF CASES.—(*Continued*)

No.	Blood examination	Family history	Treatment	Result and cause of death	Histological findings	Remarks
1	R. B. C.: 2,281,000 W. B. C.: 3,600 in last months.	Unknown.	Expectant.	Died. Tuberculosis, pulmonary and intestinal.	Spleen: Parenchyma replaced by large irregular cells with pale-staining cytoplasm in connective tissue spaces. Liver: Cirrhosis (?).	Condition unlike any known form of splenic hypertrophy.
2	.....	One sister, enlarged spleen; three other children died of tuberculosis.	Expectant.	Died. Bronchopneumonia; no tuberculosis.	Spleen: Characteristic cells. Lymph glands: do.	No note on bone marrow, liver or adrenals.
3	R. B. C.: 1,300,000 After operation: W. B. C.: 20,000 Dif. count normal.	No similar cases.	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells. Lymph glands: do.	No note on other tissues. Case similar to Case 1.
4	R. B. C.: 2,880,000 W. B. C.: 4,000 Hb.: 60 %	One sister, enlarged spleen and liver.	Splenectomy.	Died three hours after operation.	Spleen: Characteristic cells. Lymph glands: do. Liver: Cirrhosis with do. Adrenal: A few do.	No note on bone marrow.
5	At 15 years: R. B. C.: 5,000,000 W. B. C.: normal Later: W. B. C.: 4,000 Hb.: 45 %	Four out of six brothers and sisters had same condition.	Expectant.	Died. Exhaustion, pericarditis.	Spleen: Characteristic cells. Liver: do. Lymph glands: do.	
6	At 43 years: R. B. C.: 4,700,000 W. B. C.: 1,300 Later: W. B. C.: 800 Dif. count normal Hb.: 65 %	One sister has large spleen; five children of parents well.	Expectant.	Died. Tuberculosis, pulmonary and glandular.	Spleen: Characteristic cells. Liver: do. Lymph glands: do. Bone marrow: do.	Disease said to involve lymphatico-hematopoietic system, due to poisoning; possibly tuberculosis.
7	At 37 years: R. B. C.: 4,200,000 W. B. C.: 7,000 Dif. count, normal. Hb.: 92 %	.....	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells.	Constant abdominal pain after operation. Liver still large.
8	"No leukocytosis."	No history of similar condition in family.	Expectant.	Died. Exhaustion.	Spleen: Characteristic cells. Liver: do. Lymph glands: do. Bone marrow: do.	Ascites noted.
9	R. B. C.: 3,500,000 W. B. C.: 3,600 to 5,200 Dif. count, normal. Hb.: 35 %	Brother of Case 5; four out of six brothers and sisters had the same condition.	Expectant.	Died. Fracture of skull.	Spleen: Characteristic cells. Liver: do. Lymph nodes: do. Bone marrow: do.	More abdominal process than in Case 5. No tuberculosis.

10	R. B. C.: 4,700,000 W. B. C.: 3,800 Dif. count, normal. Hb.: 65 %	Three sisters and one brother had large spleens; seven brothers and sisters well.	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells.	Wassermann and von Pirquet negative.
11	R. B. C.: 2,208,000 W. B. C.: 5,000 Dif. count, normal. Hb.: 35 %	One sister has large spleen; one sister has large liver; two children are well.	Splenectomy.	Died one day after operation.	Spleen: Characteristic cells. Liver: Cirrhosis and do. Lymph glands: do. Bone marrow: do.	Wassermann negative. No tuberculosis.
12	R. B. C.: 5,200,000 W. B. C.: 4,800 Hb.: 80 %	.....	Splenectomy.	Died 12 hours after operation.	Spleen: Characteristic cells.	Two other cases reported, thought by Marchand not to be Gauchers disease.
13	R. B. C.: 3,840,000 W. B. C.: 1,400 to 900 Dif. count, normal. After operation: W. B. C.: 16,000	No history of similar condition.	Splenectomy.	Living 41 days after operation.	Spleen: Characteristic cells; not so extensive transformation as in other cases.	Probably a comparatively early case. Wassermann negative. Wedge-shaped thickening of conjunctiva.
14	Blood said to be normal in R. B. C., W. B. C. and Hb.	.....	Expectant.	Died. Exhaustion.	Spleen: Characteristic cells. Liver: do. Lymph glands: do.	Wassermann positive. Extensive changes, very similar to those in our cases.
15	R. B. C.: 5,000,000+ W. B. C.: 10,000 Dif. count, normal. Hb.: 80 %	One brother died with large spleen; two brothers well.	Splenectomy.	Living after 16 months.	Spleen: Characteristic cells.	Wassermann negative.
16	R. B. C.: 3,000,000 to 4,000,000 W. B. C.: 5,000 Dif. count, normal. Hb.: 45 %	One sister, next in age, had a large spleen; seven children well.	Splenectomy.	Living after six weeks.	Spleen: Characteristic cells.	
17	R. B. C.: 5,200,000 to 4,400,000 W. B. C.: 10,400 W. B. C.: 25,400 W. B. C.: 35,000 Hb.: 90 % to 60 %	11 children; four deaths; one similar case later, Case 18.		Died. Exhaustion.	Spleen capsule thickened, pulp friable, infiltration with large pale cells, round, oval polygonal granular cells. Blood pigment. Liver, same type cell.	Wassermann and von Pirquet negative. Special microscopical technique showed diffuse accumulation of lipoid material in large cells.
18	R. B. C.: 3,002,400 to 4,608,000 W. B. C.: 11,240; 18,000; 22,000; 6,480; 5,560; Hb.: 65 % Polymorphonuclears, 31 to 77 %; mononuclears, 67 to 21 %.	One case similar. Case 17.	Radium. slight decrease in size of spleen; toxic symptoms; reduction of leukocytes.	Died. Exhaustion.	Spleen, lymph glands, liver, all showed characteristic large vacuolated cells, some with greenish-yellow pigment granules.	Bright red spot in region of macula. Special microscopical technique showed diffuse accumulation of lipoid material in large cells.

NOTE.—Table taken from the Johns Hopkins Hospital Bulletin, xxvii, No. 299 (Jan., 1916). "Gauchers Disease. A report of Two Cases in Infants" by J. H. Mason Knox, Jr., Ph.D., M.D., H. Roswell Wanl, M.D., and Harry C. Schmeisser, M.D., Ph.D.

Gaucher's disease and von Jaksch's disease there is also enlargement of the spleen, may be misleading, though in the latter the spleen is rarely as large as in Gaucher's. In von Jaksch's disease or splenic anemia the enlargement of the spleen is more likely to occur in infancy and run a shorter course, especially because it responds to dietetic, hygienic and medical treatment. Nothing so far has been found that affects the course of Gaucher's disease. There are more changes in the blood pictures in splenic anemia than are usually found in Gaucher's disease. The lack of a feeling of distress in Gaucher's disease is characteristic, whereas in splenic anemia there is usually abdominal discomfort and the patient looks sick. Hemorrhages are more generalized and occur more frequently from the intestinal tract in von Jaksch's disease than in Gaucher's.

Gaucher's disease may be differentiated from Hanot's disease by the fact that jaundice appears early and remains constant in Hanot's, whereas in Gaucher's disease jaundice is very rare. The presence of fever and a leukocytosis are also in favor of Hanot's disease. Gaucher's disease should rarely be mistaken for either of the leukemias or for pernicious or aplastic anemia. The blood picture in all these is so different, and the fact that the lymph-nodes are usually involved. For the same reason Hodgkin's disease should produce no confusion. Occasionally Hodgkin's disease is found without enlargement of the lymph-nodes, though usually there is a marked involvement of the whole lymphatic system. The spleen is not always greatly enlarged and the liver is not usually affected. In pernicious anemia the blood picture with its definite changes in the shape and size of the red blood cells, the high color index and the extreme anemia are so typical that there should be no mistake in diagnosis. During intermissions, in leukemia there may be some cause for hesitation in making a definite diagnosis, but leukemias, at least in infants and children, are not prone to have intermissions of the type that would cause any confusion after a careful study of the blood. Krumbhaar* in the following chart has analyzed the various splenomegalies accompanied by anemia.

Treatment.—In this condition, as in Banti's disease, splenectomy offers the hope for obtaining the best results. So far, out of 11 cases that have been operated upon, four have died, and the remainder have undoubtedly improved, though it is doubtful whether the condition could be called cured, for the disease exists independently of the spleen. The findings in the liver, bone marrow and lymph-nodes would indicate that though the involvement is primarily splenic, the disease is a general one, and splenectomy performed even late in the disease will often give considerable relief. Where splenectomy cannot be performed *x*-ray or radium treatment should be instituted. The size of the spleen may be markedly reduced and if the application is properly graded, and the cases kept under careful observation, at least temporary favorable results will be gained. If Wahl† is right that

* Krumbhaar, E. B., Amer. Jour. Med. Sc., cl (1915), p. 227.

† Wahl and Richardson, Arch. Int. Med., xvii (Feb., 1916), pp. 238–259.

Gaucher's disease is primarily a metabolic disturbance, we should expect in future to get better results through dietetic measures. It may be that a continuous fat free diet, or one at least with the minimum amount of fats so as to furnish the necessary vitamins, would give the most satisfactory results. We have already pointed out the importance of dietary measures in all conditions in which the blood forming organs are at all implicated. Whether radical treatment is attempted or not, the daily routine and diet of the patient should be carefully regulated. Arsenic may be tried; iron is probably not indicated.

LEUKEMIA

Leukemia, or leukocythemia, is characterized by a persistent increase in the white blood cells, by a marked hyperplasia of the tissues from which they originate and by varying grades of splenomegaly and lymphatic gland enlargement. It is impossible often to define clearly the type of cell which is predominant though most cases may be grouped either as belonging to the lymphatic series or to the myeloid series. There are few blood conditions in which there is likely to be more confusion regarding the type of cells that may be present in the blood stream. The cells may have the appearance of normal leukocytes or they may in the main resemble unripe cells which have gained entrance into the circulation before they have matured. On the other hand, a simple increase of leukocytes cannot be considered in itself sufficient to make a diagnosis of leukemia. Cases are constantly being reported in which the counts of either the lymphatic series or the granular leukocytic cells reach such a percentage that one is inclined to make a diagnosis of a leukemia, but it is not upon the number of cells but upon their immaturity that diagnosis is decided. On the other hand, true leukemia has occurred in which there has been no increase in the number of white cells, but in which the blood picture shows the cells that are present to be immature, unripe cells, and on autopsy characteristic findings of leukemia are present, that is, a hyperplasia of all the tissues entering into the production of leukocytes.

Leukemia was first described by Hughes Bennett* in 1845 and in the same year by Virchow.† Bennett described the enlarged spleen and called attention to the large number of leukocytes in the blood. He termed the condition leukocythemia. Virchow called the condition leukemia and differentiated between the type in which the principal pathological change was in the lymphatic glands and that in which the spleen was primarily enlarged, calling one splenic leukemia and the other lymphatic leukemia. It was not until Ehrlich‡ discovered the differential stains for granular and non-granular leukocytes that a differentia-

* Bennett, J. H., Edin. Med. & Surg. Jour., lxiv (1845), p. 413.

† Virchow, R., Frorieo's Notizien, No. 780 (1845); also Med. Zeit., xv (1846), p. 157, and Zur. path. Phys. des Bluts, Virchow's Arch., v (1853), p. 43.

‡ Ehrlich, P., "Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes." Berlin, A. Hirschwald (1891).

KRUMBHAAR'S ANALYTICAL CLASSIFICATION OF CLINICAL TYPES OF SPLENOMEGALY ACCOMPANIED BY ANEMIA

	Etiology	Pathology of spleen	Family history	Time of onset	Duration	Icterus	Splenomegaly	Hemorrhages	Anemia	Resistance of red blood cells	Reticulated red blood cells	Urobilinuria	Leukocytes in blood	Liver	Treatment
Gaucher's disease.....	Toxin? Infection? Tumor?	Peculiar cell hyperplasis.	Occasionally positive.	Childhood.	Many years.	Rare.	+++	Occasionally.	Slight.	?	?	?	−	+	Splenectomy?
Banti's disease.....	Toxin? Infection?	Hyperplasia fibrosis.	Negative.	Adult life.	Few years.	Rare.	+	Occasionally.	Slight to severe.	Normal.	Normal.	+	−	First + Later −	Splenectomy.
v. Jaksch's disease.....	Rachitis?	Hyperplasia fibrosis.	Negative.	Infancy.	Several months.	Rare.	++	?	Slight to severe.	?	?	?	+	+	Splenectomy? Iron, arsenic, etc.
Hayem-Widal.....	1. Primary? 2. Secondary to infection.	Congestion and pigmentation.	Negative.	Any age.	Many years.	Present.	++	Rare.	Severe.	Diminished.	Increased.	+	−	+ or normal.	Splenectomy.
Chauffard-Minkowski...	Heredity.	Congestion and pigmentation.	Positive.	Congenital or childhood.	Many years.	Present	++	0	Slight.	Diminished.	Increased.	+	−	+	Splenectomy.
Pernicious anemia.....	Enterogenous toxin?	Fibrosis.	Negative.	Adult life.	Few years with remissions.	Very rare.	Slight or diminished.	Rare.	Severe.	Increased.	Increased.	+	− or +	Normal.	Iron, arsenic, etc. (splenectomy questionable).

NOTE.—Taken from "A Classification and Analysis of Clinical Types of Splenomegaly Accompanied by Anemia," by E. B. Krumbhaar, M.D., Amer. Jour. of the Medical Sciences, cl, (Aug., 1915), p. 227.

tion was possible between the types of cells on which to-day we base the diagnosis of the leukemias; differentiating those in which the cells are mainly granular or myeloid and those which are mainly lymphocytes or non-granular. Neither the question of the spleen nor the involvement of the glandular system is made a point of differential diagnosis, but rather the type of cell that is present in the blood. It is true that in the myelogenous type the spleen is found more often enlarged, or is larger than in the lymphatic type. For that reason it is often termed splenomyelogenous leukemia. The hyperplasia of the particular type of cell, myeloid or lymphocyte is found porliferating not only in the bone marrow, spleen and lymph glands, but may be found in almost all the tissues. A great deal of confusion has arisen from the fact that in certain cases, especially acute cases, or just before death in chronic cases, the type of cell may change from the myeloid to the non-granular type, making it appear as if there had been a change either in the type of leukemia or that there was a mixed leukemia. This, however, has been shown not to be the case, since, as Naegeli* has pointed out, the myeloblasts or pre-myelocytes resemble very closely the large lymphocytes, but they do not originate from lymphoid tissue but from myeloid tissue, as can be proven by the oxydase test which differentiates granular from non-granular cells. This has been pointed out by Myer† who was able to distinguish the myeloid character of what appeared to be large mononuclear non-granular cells as really being myeloblasts because they gave the positive oxydase reaction in two clinical cases. This test has been simplified and made more applicable to clinical use by Graham.‡ Though some of the younger forms of pre-myelocytes (myeloblasts) may not be positive by the oxydase test, yet if the blood is tested from day to day there will be found that an increasing number of these cells gives a positive oxydase test.

Leukemia has been described as occurring in various animals. In this country Tyzzer and Ordway§ have described tumors of a leukemic lymphoma in the common fowl in which lymphatic leukemia was also associated. Leukemia has also been described as occurring in dogs and in pigs. It is much rarer in cattle, though it has been reported as occurring.

Wells|| has reported a leukemia and psuedo-leukemic condition occurring in mice, but this occurs only in strains which have an hereditary history of tumors, and that in these mice leukemia behaves exactly like tumors of myeloblastic or lymphoblastic tissue.

Leukemia is far more likely to occur in males than in females and the various types of leukemia also have a predilection for different age

* Naegeli, O., "Blutkrankheiten und Blutdiagnostik." Leipzig, Veit and Camp (1912).

† Frankfurt Zeitschr. fur. Path., xv (1914), p. 40.

‡ Graham, G. S., Jour. Med. Res., xxxv (1916), p. 15.

§ Tyzzer, E. E., and Ordway, Thos., Jour. Med. Res., xxi (1909), p. 459.

|| Wells, H. G., Trans. Assn. Am. Phys., xxxi (1916), p. 170.

groups; the acute leukemias occur during infancy and young adult life much more frequently than in later years, whereas the chronic types are very much less likely to occur during infancy and childhood. This is very well brought out in figures tabulated by Ward.* From this table it is seen that acute lymphatic leukemia is far more prevalent in the first five years of life than any other period. During the period

All ages to age of	Acute leukemia		Chronic lymphatic leukemia		Chronic myelogenous leukemia	
	M	F	M	F	M	F
5	60	40	..			
10	65	35				
15	69	31	75	25	60	40
20	72	28	80	20	61	39
25	71	29	83	17	55	45
30	71	29	81	19	52	48
35	70	30	76	24	52	48
40	69	31	86	14	52	48
45	68	32	75	25	53	47
50	68	32	77	23	55	45
55	67	33	75	25	54	46
60	67	33	77	23	56	44
65	..	..	73	27	56	44
70	..	..	74	26	56	44
75	..	..	74	26	56	44
80	..	..	75	25	56	44
85	..	..	..	..	56	44

of from 6 to 10 years it falls quite rapidly, but rises again in the period of 11 to 15 and still higher between 15 and 20. After 25 the chronic type of myelogenous leukemia is more likely to occur, though acute leukemia is still quite prevalent. After 45, chronic lymphatic leukemia is more likely to occur. Undoubtedly many cases during infancy have been overlooked because of the acute course which they run and their early fatality. Pisek† could only find 19 authentic cases of myelogenous leukemia in children and only seven of these were under two years of age. Knox‡ describes a case of myelogenous leukemia in an infant nine months old and Larrabee§ reports a case of lymphatic leukemia which he saw in a child six weeks of age, and traces the symptoms back to the sixth day after birth. He suggests that the process was probably present when the child was born. William

* Brit. Jour. Child. Dis., xiv (1917), p. 10.
† Pisek, G. R., Arch. Pediat, xxxiii (1916), p. 938.
‡ Knox, J. H. M., Pediatrics, xxvii (1916), p. 74.
§ Boston Med. and Surgical Journal, clii, (1905) p. 40.

Hunter* asserts that heredity is an important factor. Holt† states that in a small number of cases heredity has been noted. Gordon Ward presents two theories, one being that the disease is a metabolic one and the other that the disease is due to intestinal sepsis. He does not think that heredity plays any part as an etiological factor, but admits the congenital type of lymphatic leukemia and reports six cases from his own observation. He does not think that it is hereditary as he gives a history of 14 leukemic mothers, none of whom gave birth to leukemic children. Wells' finding, however, that leukemia was more likely to occur in mice with hereditary strain, is suggestive.

Lymphatic leukemia is reported as following measles, syphilis rickets, and malaria and Nieman‡ states that "the presence of cherry-red spots in the maculæ resembling those found in amaurotic family idiocy suggests that the essential degeneration in the latter condition may possibly be of similar nature." Simon and Judd§ report finding the cornyne bacterium in the glands of a man aged 20 who died from acute lymphatic leukemia. This is the same organism which has been reported as found so frequently in Hodgkin's disease. Steele‖ has reported finding the same organism in the organs of a boy 12 years old with acute lymphatic leukemia.

Animal experimentation has been reported by Schmeisser¶ who was able to transmit leukemia in fowls through five generations, and by the work of Wintermitz and Schmeisser** who were able to produce a condition very like leukemia in the fowl by the injection of fowl typhoid bacillus. They found that the animals who did not die developed a blood picture characteristic of leukemia and that the organs showed a myeloid infiltration. Sellards and Baetjer†† have attempted to transmit leukemia to monkeys. They report they have been able to get an abortive type of leukemia.

Some leukemias have been considered as primary and others as secondary; primary leukemias being those in which the etiology is unknown, and secondary, those in which there was a supposed etiological factor known. It is doubtful though whether the so-called secondary leukemias are true leukemias. They have been reported as following various conditions such as the ones reported by Cabot.‡‡ Two of Cabot's cases were in children, one of six years of age and the other 15 months. In both the white counts were very high, one

* Lancet (Jan. 27 and Feb. 3, 1900), Infantile Anemias.

† Holt, L. E., "Diseases of Infancy and Childhood, Text-book." Appleton Co., New York (1920).

‡ Lymphatic Leukemia, Brit. J. Dis. Child., xl (1914), p. 448.

§ Jour. Amer. Med. Assoc., lxiv (1915), p. 1630.

‖ Boston Med. and Surg. Jour., clxx (1914), p. 125.

¶ Schmeisser, H. C., J. H. H. Reports, xviii (1919), p. 24.

** J. H. H. Reports, xviii (1919), p. 25.

†† J. H. H. Bull., xxix (1918), p. 135.

‡‡ Cabot, R. C., "Guide to the Clinical Examination of the Blood for Diagnostic Purposes." New York, W. Wood and Co. (1904).

94,000 and the other 185,000 with 64 to 66 per cent. of lymphocytes. Stevens* reports a case of bronchopneumonia in a child 22 months old with a blood count of 236,000 leukocytes, 65 per cent. of which were lymphocytes. Austrian† reports a case in a child of four with bronchopneumonia with a white count of 192,000. There were many myelocytes and unclassified cells and the autopsy showed a myeloid infiltration of the bone marrow, spleen and liver, and the bronchial and mediastinal glands were much enlarged. Hirschfield and Köthe‡ report a case of gangrenous appendicitis in a boy of 10 with duodenal hemorrhage from an ulcer, with a leukocyte count of 190,000, myelocytes 7 per cent.

The changes that occur in congenital syphilis and those which are associated with rickets, tuberculosis and intestinal infections may also produce myeloid changes which might be mistaken for leukemia. A careful study of the blood in these conditions, however, will show that the increased number of cells are usually fairly normal lymphocytes, though wheret he cells of the myeloid series are increased there is more difficulty, as is the case sometimes in congenital syphilis or tubercular infections. Some of these atypical or secondary leukemic types are illustrated in the clinical histories of cases given.

Acute Leukemia.—Acute leukemias, as has been stated, are very much more frequent in infancy and childhood than are the chronic types of anemia. However, subacute cases occur which make the differentiation between acute and chronic cases rather difficult. As a rule acute cases progress very rapidly and end fatally in a few weeks or at most one or two months. Some cases have been reported as lasting six months but in such cases there is always a suspicion that these are exacerbations occurring during the course of a chronic, rather than exemplifying the full course of an acute leukemia. In the acute leukemias, though fundamentally and histologically different, there has been in the past a great deal of confusion in classifying, or in differentiating the myeloblastic from the lymphoblastic type. This differentiation is often very difficult, but we believe that by a careful study of the blood with the modern methods, it can be made in most cases. Certain cases have been reported in which the type of cells was so embryonic that the differential staining and cytological studies were unable to place the leukemia. Such cases, of course, are only cleared up by a post-mortem examination of the tissues—this is always the court of last appeal—and, as has been said, in aplastic anemia, where the differential diagnosis cannot be made during life, tissue examination must be relied on to clear up the diagnosis. Until the last 15 years most of the cases reported were classified as acute lymphoplastic leukemias. During the past few years, however, more cases of acute myelogenous leukemia have been reported and it would appear as if their number would increase as more careful studies of the

* Stevens, J. L., Lancet, xi (1902), p. 792.
† Austrian, C. R., J. H. H. Bull., xxii (1911), p. 298.
‡ Deutsch. med. Woche., xxxiii (1907), p. 1255.

blood are made. From a clinical standpoint the two types of acute leukemia are entirely similar and as there is no difference between the prognosis and the treatment they will be considered together.

The onset is usually definite and rather sudden. The child is taken ill, has temperature and extreme prostration; the gums are often so red and swollen that they are mistaken for scurvy. With this there is a marked tendency for hemorrhage from the mucous membranes of mouth and throat. The tonsils are usually very much enlarged and may be covered with a necrotic sloughing material, which may be mistaken for a diphtheritic membrane, though it is usually a very much dirtier gray and the odor from the necrotic tissues is entirely different. The cervical lymph glands are usually enlarged; though they may not be so much as to be seen, they can always be felt. This is often true of the myelogenous type; in the lymphatic type they tend to be much larger, though they are always discrete and never matted, as in Hodgkin's disease. With this bucco-pharyngeal syndrome there is always pallor and the child looks ill. This is the reason why it is more often mistaken for an acute infection, or if the hemorrhages are predominant, may be mistaken for one of the hemorrhagic diatheses. In certain cases there may be very few other symptoms than the illustrative condition of mouth and throat, little or no glandular enlargement and no splenic enlargement. Such cases can only be diagnosed with careful study of the blood. Unfortunately in these acute cases the blood count is often found low, leukopenia being present, and this in itself should make one very suspicious. In other cases glandular swellings and splenic enlargement may be the predominant features of the condition. The physical examination often gives little else besides the findings in the mouth and throat and glandular enlargement or splenic enlargement. There may be hemorrhages into the eyes; hemorrhagic exophthalmia has been noted; hemorrhages in the fundus of the eye are frequently seen. Cranial nerve involvement, as well as intracranial hemorrhages, have been reported. There may be effusions into any of the serous cavities, pleural or pericardial; hemic murmurs are usually present; signs of cardiac weakness, rapid weak pulse, dyspnea and cyanosis on exertion are common symptoms. Enlargement of the spleen varies. It is usually palpable but never as much as in the chronic cases. It may extend down, and frequently does, as far as the umbilicus, though in acute cases it may not be felt at all. The liver is usually slightly enlarged. Gastro-intestinal symptoms are common and may be accompanied by vomiting and diarrhea, hemorrhage from the stomach or from intestines. Hemorrhage may occur in the urine, though this is infrequent, and albumin and casts are usually present. The long bones are usually tender and petechiæ are often found on the extremities.

Blood Picture.—There is a severe anemia with a markedly low hemoglobin percentage and red cell count. The hemoglobin may fall as low as 10 or 12 per cent. but often does not go below 40 per cent. The red cells also reach a very low level. There is a tendency for the

blood in this relation to have somewhat the appearance of pernicious anemia and the color index may be high. There is moderate achromia, nucleated red cells are usually present and there is definite change in the size and shape of the red cells, poikilocytosis and polychromatophilia being present. At times the red cells may not be decreased below normal in number, in fact there may be a polycythemia as in the case of acute myelogenous leukemia reported here in which at times there were as many as 7,900,000 cells, though the low hemoglobin gave the characteristic appearance of marked anemia. The diagnosis in these cases is made from a study of the white blood-cells. The total count in the acute cases is rarely as high as it is in the chronic or subacute cases. In fact, some of the acute cases may run through almost their entire course with a very low count (aleukemic). The lowest that we have seen is the one of lymphatic leukemia here reported in which the white count just before death dropped to 600, the highest count in that case being 74,000. The count may run up as high as 200,000 or 300,000 or even higher. In the lymphatic type there is a marked increase in the lymphocytes which may vary from 50 to 98 or 99 per cent. Many of these cells are abnormal in size and shape and staining quality. In the more acute cases the large lymphocytes predominate and at times many cells with pale staining nuclei, so-called Rieder cells, may be present. The azure granules in the large lymphocytes are usually decreased. The polymorphonuclear cells and granular leukocytes are markedly reduced, the eosinophils may be almost absent; this is an actual as well as a percentage decrease or reduction. Even in the lymphatic type the myelocytes may be present though usually in small number and then late. They indicate a marked stimulation or final stimulation and outpouring of the marrow cells. In the myelogenous type the first appearance is that of a marked increase in the large lymphocytes and this is the reason why these cases are most often confused with the acute lymphatic type. On careful examination, however, these cells will be found to have fine neutrophilic granules. They represent the cell in transition between the myeloblasts and so-called myelocytes. Naegeli* thinks that these are of great diagnostic importance in acute myeloblastic leukemia. They may be found in as large a percentage as 50 or 60 per cent. though usually they range from 20 to 30 per cent. The mature polymorphonuclear leukocytes may be very scarce. The eosinophilic and basophilic polymorphonuclears may be either very much reduced or absent. It is at times very difficult to make a positive diagnosis by a cytological examination between these large myeloblastic cells and the lymphoblastic large mononuclears. If, however, atypical myelocytes are present in any number, the undifferentiated or unclassified mononuclear cells may be taken as belonging to the myeloid series. These can be further classified by making use of the oxydase reaction, which identifies the cells of the granular

* Naegeli, Otto, "Blutkrankheiten und Blutdiagnostik." Leipzig, Veit and Comp. (1912).

series. This can be carried out most efficiently as described by Graham* where the smear is fixed for two minutes in a mixture of nine parts of 95 per cent. alcohol and one part of 40 per cent. formaldehyd and rinsed in water. The smear is then flooded with a solution containing a few crystals of benzidin and 0.02 c.c. of hydrogen peroxide in 10 c.c. of 40 per cent. alcohol. This is left on for 5 or 10 minutes. The slide is then washed with water and counterstained with Loeffler's alkaline methylene blue for 30 seconds. The granules of the myeloid cells are stained brown. The preparation may be kept permanently. If this is positive it is conclusive evidence that the cells belong to the myeloid series. However, the more unripe cells or more embryonic forms may react negatively. Some of the newer vital staining methods may in future assist in differentiating these earlier forms of granular cells. H. M. Evans, is now working on some of these differential stains using the various vital stains and it would appear as if there were much to be hoped from these vital staining methods in the future. On the differentiation of these earlier forms depends much of the unsettled ground between a dualist such as Naegeli and those who believe that all the cells originate from a single hemoblast. From studies now in progress in Evans' laboratory it would appear as if the dualist theory had more in its favor than the single parent cell theory.

Diagnosis.—Undoubtedly many cases of acute leukemia are not diagnosed as such because the specific character of the condition often over-shadows everything else, and where the blood is not studied cases have been recorded as acute diphtheria, endocarditis, hemorrhagic diatheses, scurvy or general sepsis with glandular involvement. The pharyngeal and tonsillar membrane often resembles that found in Vincent's angina, and, what is more confusing is that, not infrequently in true leukemia, the fusiform bacilli and spirillum are found in the tonsillar exudate; still further confusion is possible because in Vincent's angina a lymphocytosis is very common. In Vincent's angina, however, the course of the disease is entirely different. Cases are not toxic, usually have little or no temperature and clear up very rapidly under local treatment. They are never associated with the hemorrhagic tendencies which are associated with leukemia. Bleeding from the mucous membranes and the gums, epistaxis, and tarry stools are usually present in acute leukemia. Where the white counts continue low throughout the whole course it is often difficult during life to make a differential diagnosis between acute leukemia and aplastic anemia, and, as has been said, the diagnosis may only be possible after careful examination of the liver, spleen, bone marrow and lymph glands. The same is true of the differential diagnosis of Hodgkin's disease, leukosarcoma, myeloma, chloroma and tumors with bone marrow metastases which tend to give a myeloid blood picture. However, in most cases careful and repeated study of the blood with the characteristic symptom-complex (bucco-pharyngeal), associated with glandular

* Jour. Med. Res., xxxix (1918), p. 415.

enlargement, marked splenic and lymphatic enlargement and tendency to hemorrhages, makes a diagnosis fairly definitely possible.

The pathological picture is more characteristic in the two types. In myeloblastic leukemia there are slight changes in the alimentary canal and at times intestinal ulcers have been noticed. The liver is considerably enlarged due to the packing of the portal space and hepatic capillaries with leukocytes. The bile ducts are normal. The veins of the capsule of Glisson, the intralobular capillaries and central lobular vein show an enormous increase in leukocytes with rich, finely granular neutrophilic protoplasm and large eccentric nuclei.* This leukemic infiltration of the marrow is very characteristic. Giant cells of the bone marrow are usually present, and normoblasts as well as large phagocytic cells are present in the majority of cases. The spleen is usually very much enlarged, though in some of the more acute cases this is not a marked feature. The spleen is generally firm, the follicles are prominent and composed of densely packed myeloid cells. The splenic pulp is composed mainly of all types of neutrophilic myelocytes. The larger as well as the smaller veins have a very well marked leukemic infiltration into the intima. The lymphatic glands are not generally enlarged to any extent in this type of leukemia but when they are affected they are filled with myelocytes or cells belonging to the myeloid series. They often show some pigmentary changes. Though they may not be enlarged most of the lymph glands will show the presence of myeloid cells. The thymus is at times invaded with the typical myelocytes. The bone marrow throughout the body shows marked hyperplasia and the marrow of the shaft is soft and pulp-like and has a peculiar pinkish or yellowish brown color. The fat marrow everywhere has disappeared. Large giant cells with an irregular outline and a somewhat granular protoplasm are numerous. Myelocytes are enormously increased, the eosinophilic type being present always in large numbers. Basophilic myelocytes are present to a less extent. Red blood-cells and nucleated red cells are few. The erythroblastic tissue as a whole tends to disappear and is displaced by the myeloid cells, as also are the megacaryocytes, so that there is a marked reduction in the output of platelets as well as red blood-cells. The other organisms show varying amounts of myeloid cell invasion. In the lymphatic type the essential histological picture is an over-production of the lymphocytes which migrate from the blood stream and infiltrate practically all the organs and tissues except the central nervous system. In the majority of cases the lymphatic glands are enlarged though we have seen acute cases in infants without any enlargement of the superficial lymph glands. The glands remain discrete and do not show the matting and clumping so typical of Hodgkin's disease. The glands are often packed with lymphocytes often to such an extent that the cortex and medulla of the gland is so fused that differentiation is lost. The blood-vessels are dilated and their typical arrangement is lost. Germ centers can no longer be found. The lymphocytes show remark-

* Karsner, H. T., Univ. of Pa. Med. Bull. (Jan., 1910).

able activity, their nuclei often branching. Large phagocyte cells and giant cells are sometimes found in the pulp. The hemolymph glands lose their characteristic appearance and cannot be differentiated from other lymph glands. The thymus is generally not affected very markedly, though infiltration of the thymus has been noted in several cases. Rocasz* reports a case of acute lymphatic leukemia in a child of four years with a marked enlargement of the thymus which measured 12 × 10 × 4 cm. and weighed 200 gm. Serard† reports a case of a girl of five with a thymus weighing 150 gm. and measuring 8 × 6 cm. Both Serard and Obrastow‡ have reported cases in older children, one 16 years and the other 17 years of age, with enlarged thymus. The spleen in acute lymphatic leukemia is usually enlarged though not to the extent that it is in acute myelogenous leukemia. At times it may not be palpable or is very slightly so. In the more chronic cases it extends very often into the pelvis and fills the whole left side of the abdominal cavity reaching beyond the median line, and resembles very closely in appearance that of the spleen in chronic myelogenous leukemia. The surface of the spleen is hard and smooth and notches may be felt with ease. The Malpighian bodies are generally atrophied. The pulp is packed with lymphocytes. The endothelial cells, the large phagocytic cells and giant cells of the bone marrow may all be present in large numbers. Pigmentation and fibrosis may be present in some of the more chronic cases.

The normal yellow marrow and fat of the long bones has usually disappeared and is replaced by pinkish or brownish yellow marrow which is composed mainly of lymphocytes both large and small. The decrease in the red blood-cells and normoblasts is usually not as marked as it is in acute myeloid leukemia. The liver is often infiltrated by large numbers of lymphocytes which may be visible under the capsule and along the portal system. In extreme cases, the hepatic cells may appear as islands lying along the invading lymphocytes. Giant cells and large phagocytic cells are not constant. The liver may not be very much enlarged usually having a fatty appearance. There is usually an excess of pigmentation around the periphery of the lobules. The kidneys are usually enlarged due to the lymphocytic invasion. Hemorrhages often occur in the kidneys which give rise to the piebald appearance. There may be atrophy of the glomeruli due to the pressure of the lymphocytes. The main seat of proliferation is undoubtedly the bone marrow. In acute cases the remainder of the lymphatic system, lymph glands and spleen, may not be affected and even microscopically show very little change. In these acute cases anemia is the most pronounced symptom and the cause of death because red blood-cell production is almost entirely replaced by the increase of lymphocytes. The new bone marrow production is so far given over to producing lymphocytes that only badly formed red blood-cells make their appear-

* Rocasz, Jahrb. f. Kinderh., lvii (1903), p. 242.
† Serard, L., Thèse de Paris (1900).
‡ Deutsche Med. Wchnschr., xvi (1890), p. 1150.

ance with normoblasts and megaloblasts. The anemia is still further increased by the phagocytic action of the large lymphocytes and endothelial cells. Hemoglobin from the destroyed cells is deposited as iron either in the organs where it is broken down, or is taken up by the general circulation and carried to the liver cells. In the chronic cases where the lymphatic proliferation is not only in the bone marrow but in the lymph glands and spleen there is a greater production of red blood-cells in the bone marrow than in the acute cases and therefore the anemia is less marked. This over-production of lymphocytes undoubtedly affects the proper functioning of many organs. The organs affected often vary. Sometimes the alimentary canal is definitely involved, in other cases, only slightly involved. The liver and kidneys are usually affected to such a degree that their functioning is seriously interfered with. The lowered resistance to infection which is such a prominent feature in lymphatic leukemia is easily accounted for by the diminished production of polymorphonuclear cells. This accounts for the high mortality by general sepsis or anemia. Hemorrhage, especially from the mucous and serous membranes, is especially prominent in lymphatic leukemia, probably more so than in myelogenous leukemia, because the platelets are more often markedly decreased. Hemorrhages may occur in the central nervous system; subdural and meningeal hemorrhages are common though usually not enough to cause definite symptoms.

What encourages the over-production of lymphocytes we do not know for certain. No organism or toxin has been constantly demonstrated. Even infections of various types, which have sometimes been claimed to be the direct cause of stimulating this over-production, are lacking. The most possible etiology of the disease is that it belongs to the group of malignant tumors; in fact, swellings of the gums and glands are not uncommon. These swellings or tumors are evidence of the wild overgrowth of myelogenous or lymphoid cells. The condition is always fatal, which corresponds to the end result of tumors rather than infections. Whatever the cause of the disease there can be no question that there is an overgrowth of either myeloid cells or lymphoid cells. This may be due to a stimulation primarily of the bone marrow, or to the withdrawal of the normal resistance to over-production, which is always present in every organ and which keeps the balance of activity of the organ as a part of the whole.

In the subacute or chronic types of either myelogenous or lymphatic leukemia, the onset is somewhat slower. In these cases the enlargement of the spleen or of the lymph glands is very much more marked. The spleen may fill the whole of the left abdomen and reach over on to the right side. The individual glands may be very large and almost every gland in the body may be involved. The most obvious glands are those in the cervical region, and these may so fill out the neck that the dimensions of the neck may be as large if not greater than the head or face dimensions. Axillary, inguinal, bronchial, peritoneal and retro-peritoneal glands may all be greatly enlarged. The liver is

also usually larger. In the chronic cases the condition may remain for comparatively long periods in a quiescent stage and then the progress may be very rapid so that intervals of rest and progress may alternate over long periods. In other cases the progress seems to be slow but steady. The outcome in these cases often at the end resembles that found in the acute type. There is always progressive weakness and often a secondary infection causes the fatal termination or prolonged severe hemorrhage. The blood picture in the subacute or chronic cases is not very different from that of the acute type, though on the whole the number of white cells tends to be greater and there is less likely to be a marked increase in the younger forms of unripe cells, and the predominating cells, whether myelocytes or lymphocytes, tend to be more characteristic.

The small lymphocytes in chronic lymphatic leukemia tend to predominate over the large, though variations in this will appear from time to time. During exacerbations this is particularly true. It is often impossible to place the cells between the small and large lymphocytes, as there are so many transitional forms. In the more subacute or chronic cases of myelogenous leukemia, the type of myelocytic cell may vary considerably between the neutrophilic, eosinophilic or basophilic and on different occasions the variations among these types of cells may be very extreme. The blood platelets in myelogenous leukemia are usually increased. We have seen a complete shower after benzol treatment, in which the platelets went up to 1,120,000 and there was rapid clotting of the blood during this period. (This case is referred to in full.)

The number of cells varies from day to day for no special reason. During febrile infections, especially those of the upper respiratory tract, the count in any type of leukemia may fall from 200,000 or 300,000 to 8000 or 10,000 in a very short time.

Prognosis.—Prognosis is always fatal during infancy and childhood. Even chronic cases do not usually live many months. Few cases have been reported as living longer than two years, the majority die in less than 12 months. The myelogenous type are likely to live longer than the lymphatic type and tend to have more remissions, during which the blood picture may come back almost to normal. Under treatment in the chronic cases the enlarged spleen may diminish in size and the glands in lymphatic cases may almost entirely disappear. The liver becomes smaller. The red blood-cells and hemoglobin return approximately to normal. The increased number of white cells, whether myeloid or lymphocyte, may remain as the only indication that the condition of leukemia is present. This rarely returns to normal and atypical cells are always to be found. We have never seen the white picture return to normal during a remission. In the acute cases the whole duration of the condition from the time of the first suspicion to the fatal end may be as short as one or two weeks. Terminal hemorrhages are not infrequent in these cases. The varying leukocyte count in these acute cases does not mean a betterment of

the condition. The course is always progressively fatal, usually rapidly so, in the acute form. We have never seen an acute case become chronic. The reverse of course is not true, as chronic cases tend to become acute, and end usually in such exacerbations.

Differential Diagnosis.—The diagnosis in acute cases is sometimes complicated with the question of acute infection. The throat and tonsils may suggest, as has been said, diphtheria or Vincent's angina. The acute hemorrhages may suggest either an acute purpura hemorrhagica or one of the infectious purpuras. In the more chronic cases diagnosis is at times confused with such conditions as Hodgkin's disease, though the glands in Hodgkin's disease are usually very much more enlarged and are matted together. The blood picture is entirely different. Some of the tumors of the bone marrow or leukosarcoma may give a blood picture which at times resembles that of acute leukemia. It may be impossible to make a diagnosis during life but usually the primary focus can be made out. A careful study of the blood, frequently repeated, in all doubtful cases, is the best means we know of for making a differential diagnosis.

Metabolism and Chemistry of Blood in Leukemia.—Most of those who have worked on the metabolism of the blood in leukemia are agreed that there is a marked rise in the basal metabolism. Murphy and Means* think this is due to the great quantities of lymphocytes or myeloid cells which are continually being formed or broken down. During this breakdown they liberate large quantities of nucleoprotein materials, such as purin, uric acid, zanthin, hypozanthin and phosphoric acid. Leukemia has been termed a nitrogen and phosphorus disease, because of their marked retention. Murphy and Means from their own work, and from calculations made from metabolic studies found in literature, estimated that the increased metabolism in lymphatic leukemia is 52 per cent. above normal, and in myelogenous leukemia, 44 per cent. This high metabolism may be accounted for by three compensatory factors; that is, while there is reduction in the hemoglobin the blood supply to the tissues may be greater, due to increased rate of blood flow, or there may be greater complementary ventilation. The hemoglobin certainly in leukemia does not vary from normal hemoglobin; it is simply a difference in quantity, not in quality. If these compensatory factors are not sufficient to explain the increased metabolism, we may attempt to do this by assuming that the increased metabolism is produced by the fact that young immature cells are appearing in the blood due to the large number of white blood-cells. As has already been pointed out, young cells have an increased oxygen consumption. This was pointed out in connection with reticulated cells. But the increased metabolism in leukemia cannot by any means be accounted for alone on this assumption. The increased number of white cells as shown by Murphy and Means, and Aub, also show a parallelism to the increased

* Murphy, J. B., and Means, J. H., and Aub, J. C., Arch. Int. Med., xix (1917), p. 890.

metabolism though when there was a reduction in the leukocytes there was not such a marked reduction or lowering in the metabolism.

In acute leukemias there is always a negative nitrogen balance. In the specially acute or chronic ones there is more variation and they may show little or no signs of increased protein catabolism. In the acute cases the nitrogen elimination may exceed the intake. Magnus-Levy* found there were 40 more grams of nitrogen eliminated than were taken in, whereas Musser† found an output of 22.28 with an intake of only 7.25 gm. These workers also found very marked phosphorus retention, since the leukocytes destroyed contained so much phosphorus, and they explained for this same reason the excretion of uric acid, purin bases and phosphorus due to the breakdown of a nuclein product.

This is certainly true of the acute cases, while in the chronic cases there is more divergence of opinion. This may be accounted for by the fact that in chronic cases the disease is for periods apparently at a standstill. During these periods of remission the elimination of nuclein products may not be very high. As might be expected from the type of cells which predominate more positive findings have been reported in myelogenous leukemia than in lymphatic leukemia as the granular cells contain more nuclear material. This is apparently true of the elimination of uric acid.

In acute cases this may run as high as 0.655 and 0.523 in grams of uric acid nitrogen excreted. As shown in two cases studied by Magnus-Levy‡ the figures for uric acid nitrogen output in chronic myelogenous leukemia are greater than those for chronic lymphatic leukemia, as might be expected. In chronic lymphatic leukemia, in fact, it may not be very much increased over the normal limits. The other non-protein nitrogen constituents, urea, ammonia, amino acids and creatinin, vary usually within normal limits. During treatment by *x*-ray or radium, as has been pointed out by Ordway§ and by Knudsen,‖ the total nitrogen, urea, ammonia and phosphates are markedly increased. This increase begins immediately and is at its maximum about the end of the seventh day after which it decreases slightly. Most of these products do not reach normal but remain somewhat above the point where they were before treatment was begun. The phosphates in particular remain high and do not fall as much as the others. The blood during this same period of treatment and after treatment with radium showed that there was a slight increase in the non-protein nitrogen but no apparent change in the creatinin in the blood. These results are mainly from cases of chronic myelogenous leukemia and it is doubtful whether in acute leukemia the same results would be found.

* Magnus-Levy, A., Virchow's Arch. für path. Anat., clii (1898), p. 107.

† Musser, J. H., and Edsall, D. L., Univ. of Penn. Med. Bull., xviii (1905), p. 174.

‡ Virchow's Arch. für Path. Anat., clii (1898), p. 107.

§ Ordway, T., Tr. Assn. Amer. Phys., xxxi (1916), p. 177.

‖ Knudsen, A., Boston Med. and Surg. Jour., clxxvi (1917), p. 503.

The iron metabolism in leukemia snows a markedly increased excretion of iron. This is probably due to the fact that the spleen is so involved that it is unable to store iron. Following *x*-ray treatment the iron output may be tremendously increased, which is partly due to destruction of leukocytes, but also more probably to the destruction of red blood-cells which results from both *x*-ray and radium treatment. The output of calcium and magnesium varies considerably, sometimes it is greatly increased and sometimes decreased. It is usually not as high nor as constant as the great elimination of phosphoric acid in the urine. The sulphur compounds in the urine usually parallel the output of nitrogen.

Various Other Changes Which Occur in Leukemic Blood.—The phagocytic power of the leukocytes is greatly decreased as is their opsonic power. The polymorphonuclear cells do not entirely lose this power but they become very much weaker, and as would be expected, these are changed more in the lymphatic type than in the myelogenous. The more unripe or younger forms of leukocytes are present, the more feeble will be their phagocytic or opsonic power.

The production of antibodies is also lowered as has been lately re-affirmed by the work of Howell* who concludes that in the disease of leukemia individuals have lost the ability of "antibody formation" and "this loss of ability may be due to the excessive proliferation of the hematopoietic tissues, one of whose functions is the formation of antibodies. With rapidly repeated cell generations the cellular energy used in multiplication prevents the utilization of the energy which is necessary for normal function."

Ordway and Kellert† have shown that the hemolytic complement of serum in the plasma of leukemic blood is not increased. It was thought that if the complement was produced by the activity or by the breaking down of white blood-cells, it might be increased in cases of leukemia. They did not find this to be so, however. In the same way the ability of antibodies in leukemic blood is reduced. Moreschi‡ tested this out in 10 cases of leukemia by injecting the typhoid vaccine. He was not able to detect the formation of glutinins. These facts probably account for the severe results from infections in leukemia. Packard and Ottenburg§ believe that there is a leuko-toxic factor constantly present in leukemic blood, and that this accounts for periodic aleukemic phases, or periods during which the leukocytes are very much reduced. They believe that in leukemia not only over-production but increased destruction of leukocytes is constantly going on, and the number of leukocytes present at any one time therefore would depend on whether the leuko-toxic substance had the upper hand or the over-production predominated.

* Howell, Kath. M., Arch. Int. Med., xxvi, No. 6 (Dec. 15, 1920).

† Ordway, T., and Kellert, E., Jour. Med. Research, xxviii (1913), p. 287.

‡ Moreschi, C., Zeit. für Imm. Forsch. und Exp. Therap., orig., xxi (1914), p. 410.

§ Packard, M., and Ottenberg, R., Jour. Amer. Med. Assoc., lxviii (1917), p. 954.

A great deal of work has been done with ferments which are present in the blood in cases of leukemia, particularly myelogenous leukemia. Longcope* has shown that the polymorphonuclear leukocytes contain enzymes which are able to digest coagulated blood serum. It has been shown that the cells from acute lymphatic leukemia may contain a proteolytic enzyme whereas the small lymphocytes do not possess this enzyme. This can be further demonstrated by the oxydase test as already described.

Treatment of Acute Leukemia.—The course of the disease is never materially influenced by anything that can be done. The various symptoms as they arise must be treated separately; the general hemorrhages offer the greatest difficulty. Transfusion at times apparently is not able to check this even for a short time. Local application of cephalin may assist in checking hemorrhages from the mucous membranes of the mouth and nose, but in our experience one gets little or no results from any measures. Adrenalin is of no avail. Local application of perchloride of iron may be of some use in controlling small local hemorrhages, but when the oozing is general its application is most disagreeable. All the measures for making a patient comfortable should be instituted but *x*-ray, radium, benzol, arsenic, which are of avail in chronic cases, cannot be used with any success in acute cases. There is no harm in trying them but we have often felt after their application that the end was hastened rather than lengthened. This is difficult to say, however, as acute cases often terminate suddenly.

Treatment for Chronic or Subacute Cases.—In these forms there is very much more hope of treatment having some definite effect. Symptomatically, a great deal can be done to make the patient more comfortable. The anemia associated with leukemia may often be benefited by giving arsenic in Fowler's solution, starting in small doses and increasing to the point of physiological effect. Cacodylate of soda or neo-salvarsan may be given. Iron in the form of freshly made Blaud's pills is perhaps the best form of iron for these cases. The main results, however, must rest on properly graded doses of radium or *x*-ray. Before this came into use benzol was used quite freely following Selling's† experimental work with benzol. Numerous favorable reports have occurred from time to time in the literature. Billings‡ pointed out that with benzol often one obtained good results but on the other hand one often obtained very disastrous results. When the leukocytes begin to drop one must watch the effect of benzol most carefully and when the count reaches 20,000 benzol should be stopped. The effect of benzol is better in chronic myelogenous leukemia than in chronic lymphatic leukemia. If benzol is pushed too far there will not only be a reduction of white cells but also a destruction of red cells, so that one has to be careful to give doses which will bring down the white count gradually and in such cases there is often a stimulation of

* Longcope, W. T., and Donhauser, J. L., Jour. Exp. Med., x (1908), p. 618.
† Selling, L., J. H. H. Bull., xxi (1910), p. 33.
‡ Billings, F., Jour. Amer. Med. Assoc., lx (1913), p. 495.

the red cell, for benzol has a powerful stimulating effect upon the medulla of the bone. The cumulative effect of benzol is probably the most dangerous factor in its administration. It should never be given when there are acute symptoms or when there is any marked elevation of temperature. Benzol is given in capsules coated with salol containing from 0.1 to 0.3 gm. of benzol with equal parts of olive oil. If given in this way the irritating effects of benzol on the gastric mucosa are eliminated. Often if benzol is not given in capsule form there is much gastric irritation, tasting and smelling of the benzol, burning of the stomach and other disagreeable symptoms. The capsules are gradually increased in number, starting with one a day and increasing daily until 5 to 10 capsules are taken, a maximum of 3 gm. a day being administered. The capsules should be taken immediately after meals and it is important that cases taking benzol should be under careful observation. Daily blood counts should be made, and, as stated, when the white count reaches 20,000 or 25,000 it should be stopped. There can be no question that in chronic leukemias found in adults, benzol treatment is of considerable value, but in the chronic or subacute types of leukemia in children, after having tried it in a number of cases, we feel that unless the child can be kept in the hospital and watched most carefully, benzol is not a safe drug to administer, though if carefully carried out in the most chronic cases under hospital supervision, it may be tried. The results, however, from *x*-ray and radium are so much better controlled that we believe that either of these is preferable to benzol.

X-ray treatment of both types of leukemia was reported by Beclere* in 1914. He had been using this type of treatment over a period of 10 years. The condition in a large proportion of the cases was improved. The spleen and glands diminished in size. The blood picture often returned to normal or nearly normal. Symptomatically the patients felt better. Their appetite increased as did their weight, but in no case was the disease ultimately conquered. The patients all died. Recurrences or exacerbations can be checked and if the blood is followed carefully in these cases and repeated courses of *x*-ray given at appropriate intervals life can be considerably lengthened and certainly made much more comfortable.

The method of treating with *x*-ray has been lately very greatly improved. The principle of cross-fire and filtration has been brought into use. The idea of cross-fire and filtration is to have the rays reach as deeply as possible with the least possible injury to the skin, so that rays are sent in at different angles through a large number of different skin areas. In this way the spleen or bone marrow can be treated anteriorly, posteriorly or laterally. Such treatment, however, should never be undertaken by anyone except those most familiar with *x*-ray treatments. The softer rays are filtered out by an aluminium screen or a heavy piece of leather. Notwithstanding all the refinements in *x*-ray treatment there are a certain number of cases that are refractory and

* Beclere, A., and Beclere, H., Tr. Internat. Cong. Med. London (1914).

there are a certain number which show toxic symptoms very much like those following benzol, that is, a rapid fall in the white count with practically an aplastic condition supervening and often ending fatally.

Within the past few years radium treatment has been advocated by a number of workers. Most of this work has come from instances where radium has been available for use on a large number of cases. The effect of radium is very much the same as that of *x*-ray. There is a reduction in the size of spleen and glands and improvement in the blood picture. The same principle of cross-fire and filter must be used with radium. The section over the spleen or bone to be radiated should be well mapped out and the application of radium so regulated that a large area is covered without repeating any one series so that there is no possibility of using the same area twice in the same series. The areas covered are approximately 2 cm. by 2 cm. Each treatment should last from four to six hours depending upon the amount of radium used. If from 50 to 100 mg. of radium are available, treatments should be repeated once in about four to six weeks. There is some difference of opinion as to whether the long bone should ever be radiated, just as good results having been returned from limiting the treatment to areas over the spleen as when the long bones are treated.

It is important in all these methods of treatment to follow the blood curve and whenever the white cell count drops to 15,000 or 20,000 the *x*-ray or radium treatment should be stopped in the same way that benzol treatment should be stopped. If the white count has gone down as far as 15,000 there is more than a tendency for it to continue dropping and with the approach of leukopenia there is more danger of hemorrhage.

After careful study of radium treatment in leukemia, Ordway* gives conclusions concerning the value of radium treatment as follows:

"1. Surface applications of radium in leukemia produce striking, indeed remarkable improvement in (*a*) the blood picture which becomes almost normal, (*b*) in the size of the spleen and glands which are reduced almost to normal, (*c*) in the general condition of the patient who from an emaciated and weak condition may become plump and strong.

"2. The duration of remission is valuable; it may last from months to years.

"3. The results of radium treatment are not regarded as curative. It is believed to be, however, the safest as well as the promptest palliative measure in cases of chronic leukemia whether refractory or not to benzol or *x*-ray treatment. From the results of radium therapy in leukemia it is believed to be the best form of treatment now at our disposal."

At the Mayo Clinic following radium treatment, Giffin† reports a number of cases that have had splenectomy performed. Out of 18 cases they have had one death. This may be an added step toward aid in

* Ordway, Thos., and Gorham, L. Whittington, Oxford Medicine, ii, p. 751.

† Giffin, H. Z., Med. Rec., cxiv (1918), p. 1020.

prolongation of life, but even after treatment with radium and splenectomy the disease may recur. In the more chronic cases of myelogenous leukemia it is hoped by this means that a marked prolongation of life will be accomplished. Peabody's* reports agree with Ordway's conclusions and with those of Giffin. There can be no question that as the use of radium is better standardized and as we diagnose cases of chronic leukemia earlier, better results will be obtained in their treatment.

Transfusion, as has been stated, in such conditions of leukemia can only be considered as a stop-gap procedure, but it may be very valuable in tiding over an acute period so that the *x*-ray or radium treatment can be applied. What type of treatment is best in each individual case will have to be studied; the stage of the disease, whether it is progressing slowly or rapidly must be considered, and the general condition of the patient taken into account.

Unusual Forms of Leukemia.—With the modern laboratory means of differentiating lymphoid leukemia from myeloid leukemia there seems to be no reason why, in the subacute and chronic cases at least, a sharp line of differentiation cannot be drawn. There are in each group, however, atypical cases in which the grade of hyperplasia of the lymphocyte or myelocyte cells varies from being a very slight increase, or slight hyperplasia, to a very extensive hyperplasia, which may take on the form of tumors. Such tumors have been particularly reported as occurring on the scalp.

It must be remembered that the final diagnosis cannot always be made by a blood picture, especially in atypical cases, though often here, if the cases can be followed long enough and careful differential work can be done on the blood, a positive diagnosis can usually be arrived at; but the ultimate diagnosis always rests on the pathological findings. It has been pointed out that malignant tumors produce at times blood changes that may resemble leukemia, especially the aleukemic phase of a leukemia. This, of course, is due to the fact that tumor cells crowd out the blood-forming tissues in the bone marrow and so the blood picture takes on the appearance of either a lymphoid or myeloid leukemia with a low white count. In such conditions numerous atypical or unripe cells are also found in the circulation which makes the differentiation even more difficult, though usually the primary tumor can be located. This difficulty does not arise nearly as often in children as it does in adults. In the acute type of leukemia, however, the case may run with a very low white count throughout the entire course. In such cases it is the type of cell which is present which determines the diagnosis rather than their number. If there is a large percentage of atypical lymphoid cells with occasional myeloblasts and nucleated red cells, the diagnosis, taken in conjunction with the general picture of the child, who usually has the appearance of an acute infection, is made possible.

* Peabody, F. W., Boston Med. and Surg. Jour., clxxvii (1917), p. 873.

During the acute infectious diseases, however, one often finds a blood picture which may be mistaken for myeloid leukemia due to the fact that myelocytes, often as high as from 10 to 20 per cent., will be found, and often at autopsy various organs may show myeloid infiltration to a slight degree, but the process is not widespread nor does the bone marrow show the typical leukemic picture of a wild over growth of myeloid cells.

We feel, therefore, that there is no place for the loose terms "mixed leukemia" or "leukanemia."

Chloroma.—Chloroma is another type of anemia in which besides the leukemic blood there are tumors or nodules found variously located over the body and a special tendency to localize around the orbit and to involve the periosteum. The green color of these tumors is sometimes found but not always.

Chloroma resembles more nearly the acute type of leukemia though here again, both types, myelogenous or myeloid chloroma and lymphoid chloroma, may be differentiated. The lymphoid cells are usually of the large mononuclear type which must be carefully differentiated, by using the oxydase reaction test, from the myeloid series. Since this test has come into wider use fewer cases of the lymphoid series are being reported and a larger number of myeloid. This is also true of the acute type, especially in older children and young adults, though of late more acute myeloid cases have been reported in infants. Most of the cases of chloroma have occurred before the end of adolescence and a greater number in males than in females. At times it is difficult to differentiate these cases from myeloid or lymphatic leukemia and perhaps there is very little reason to do so. The spleen is usually not as large as that found in lymphatic, and certainly not as large as that found in myelogenous leukemia. The lymphatic glands throughout the body are enlarged. At times the greenish color which is, when present, so typical, may be found in these glands with the same involvement of the gums and lymph follicles of the throat and the lymph follicles of the intestinal tract are also enlarged. The tumors are found more frequently attached to the periosteum of the bone of skull and face, but may be found attached to the periosteum of any of the bones throughout the body. The tumors on section have a round cell infiltration. They may be either large lymphocytes or they may belong to the myeloid series. Neutrophils and eosinophils are also at times found and basophils only occasionally. Most of the organs show the same picture microscopically as that found in leukemia.

There has been a great deal of debate as to the pigment. It fades on exposure to the air and cannot be differentiated microscopically, as it has disappeared from the sections. It is supposed to be a fatty acid combined with the iron. The color can often be restored to the tissues by reducing agents such as hydrogen peroxide. It is nonsoluble in alcohol, chloroform or ether, and is only partly soluble in 3 per cent. acetic acid solution and boiling water.

Symptoms.—The onset is insidious, as it is in all leukemias except the most acute. The first signs are the presence of the tumors or hemorrhages from the gums. As the condition progresses the appearance of the tumors, especially about the head and face, is very striking. The eyelids may become involved so that the patient is not able to close his eyes. At times a greenish-yellow film has been described as growing over the conjunctivæ and causing practical blindness. Growths may occur in the middle or internal ear, causing deafness. Intracranial growths may give symptoms of sinus thrombosis, compression of the brain or cranial nerve involvement. The nerve tissue is not involved but merely compressed. The nodules vary from the size of a small milia to that of half a dollar and usually have a flat top. They are freely movable and painless. Associated with the tumor is the tendency to hemorrhage and this is especially marked in the gums and mucous membranes. Retinitis and optic neuritis may occur from hemorrhage. The blood changes are those found in leukemia. The number of white cells is usually not increased to anything approaching the number found in lymphatic leukemia, and the white cell count may be as low as 8000 or 10,000. The type of cell present must be carefully differentiated by all the modern methods of differentiating myeloid and lymphoid cells. The outcome in these cases is always fatal. No cases have been reported of true chloroma which have permanently recovered.

Treatment.—The treatment in these cases is the same as that for leukemia. True tumors, such as myelomata, are to be considered more as true tumor growths. They usually limit themselves to the periosteum, but when they metastasize are found as definite tumors in other organs, such as the lymph nodes, liver or spleen. The blood in such conditions shows no change, or may show definite pictures which resemble at times either lymphatic or myeloid leukemia.

The leukosarcomas, or lymphosarcomas, are probably to be regarded as true tumors. The fact that they develop as rapid proliferations either in the lymph nodes or in the mucous membranes and metastasize like true leukemic tumors differentiates them from true leukemia. There is rarely a generalized hyperplasia, which is characteristic of leukemia. The blood may show no change or one may find blood pictures which resemble an aleukemic stage of leukemia, that is, low white count with atypical cells. The final diagnosis at times may not be possible until pathological study of the disease is complete.

There are cases with hyper-mononuclear leukocytosis or so-called "infectious mononucleosis" which resemble very closely the blood picture of leukemia at first sight. These cases have been reported more frequently of late and tend to appear in children during upper respiratory tract infections or during the acute infectious diseases, especially those in which one is likely to get a change in the differential count, as measles or pertussis. In such cases often a leukocytosis with marked increase in the lymphocytes will be found which, at times, gives a slight increase in the lymph glands, and perhaps a slightly

enlarged spleen will confuse the true condition and make diagnosis rather difficult. Sprunt and Evans* have recently reported a series of cases in young adults which show an increase in the mononuclear cells, usually of the large lymphocytes, with a total increase of the cells amounting at times to as much as 20,000. These cases all recovered within a few weeks and showed a fairly definite syndrome, malaise, temperature, swelling of cervical glands and occasional swelling of inguinal and axillary glands. Tonsillar or pharyngeal involvement of the upper respiratory tract infection was more common than any other. The course ran usually from two to three weeks with complete recovery. They have been able to follow some of these cases for several years and also to observe their blood reaction in other infections. In none of these cases has there been any recurrence. Such a condition is often found in childhood but these cases are usually not confused with leukemia. There are, however, certain cases that occur more rarely in which the blood picture is more nearly that of a true leukemia in that the white count is considerably higher and the percentage of lymphocytes is that of a true leukemia. We have had opportunity of following such a case for over a year:

Ernest S. (U. of C. Hospital, No. 4330) came to the hospital when he was four years old in September, 1919, for observation after a fall upon the head. His father and mother were themselves both well, although tuberculosis had affected members upon both sides of the family. His older brother, and sister two years younger were both well. The child had a natural full term delivery, and weighed 6¼ lb. at birth. He was breast fed for five months and had never suffered from gastro-intestinal difficulties until two years of age, when he fell downstairs, rolling 22 steps. This event was followed by a severe illness of two weeks duration, in which watery green stools and "spasms" were the most prominent symptoms. Since that time cyclic monthly vomiting, lasting for two or three days, and accompanied by diarrhea and fever had been a regular occurrence. A chronic impetigo began when he was one month old, and had continued unimproved until his hospital sojourn. The accident which brought the case to our observation was a fall from a second story porch to a paved yard below. Physical examination revealed several unexpected features, with surprisingly few local signs which could be attributed directly to the fall. The boy was a well-nourished youngster, able to stand, run and walk normally. The left frontal region exhibited abrasions and swelling of cellular tissue, the eye-lids were purple and swollen, and the conjunctivæ congested and hemorrhagic. Many impetigo spots and a few scratches due to the fall were found distributed over the body and extremities. The eyes reacted normally to light and accommodation. Subsequent examination of both retinæ revealed edema and signs of optic neuritis. *X*-ray plates disclosed no abnormalities in bones of the head, thorax or extremities, but revealed a slightly enlarged heart and a bronchial marking more than normally distinct upon the right side. This seemed to be due to a peribronchial thickening of the lymph nodes. The superficial lymph-nodes and the spleen were not enlarged. Laboratory examination of the stools showed intestinal flora of the normal proteolytic type. Von Pirquet, Wassermann and blood culture tests were negative, but a surprising blood picture was observed and counted almost daily during the hospital stay from Sept. 11 to Sept. 24. The white cell count, as seen, is 55,600, 82 per cent. of which are small lymphocytes. The cells themselves were of normal appearance, and at his first examination there were no abnormal cells present. His blood was followed very carefully during a stay of 13 days during the whole of which time the white

* J. H. H. Bull., xxxi (1920), p. 410.

blood count remained high. There were no subjective symptoms. He seemed perfectly well. His hemoglobin and red count as seen was high and fairly normal and the fact that the white cells themselves did not seem abnormal in either shape or form or color and that there were no abnormal cells made us hesitate in considering him a true case of lymphatic leukemia. He returned to the hospital again in October at which time, as will be seen, his white count had returned almost to normal. We have followed him periodically since then, he having been in hospital six times during the past year. As will be seen his blood picture is not entirely normal but is practically so. There is no increase in his lymph glands. His spleen has not been felt at any time. He has had no temperature. He has had his tonsils taken out as we felt they might be a source of infection, though they were not found diseased. There was no increase of lymphocytic infiltration. They were apparently normal hypertrophied tonsils. He has gained in weight and looks the picture of health. His large lymphocytes have most of the time during the past year been above normal. His platelets have always been normal except on one occasion when they were found to be 84,000. His blood chemistry has always been normal. There is not any increase in his urea, creatinin or uric acid. He has never had any hemorrhages and during the past year he has not had a single infection or intestinal upset. Undoubtedly during his first observation period there must have been some functional derangement of the blood-forming organs which apparently affected the lymphocytes (Table 294A).

As has been said, this has been reported many times and it has been found that after injuries of the bone following fractures, or gun-shot wounds that involve the bones, a picture of this kind has at times occurred; as also after attacks of tonsillitis, or pharyngitis. During the first observation period of cases one is often perplexed, but if such a case is kept under observation there should be no difficulty in making one's mind clear as to the true diagnosis. In the type of case under discussion there are few or no pathological cells found. This differs very markedly from the leukemias in which a large percentage of the cells are immature, unripe or early cells. This is clearly shown in the following two histories, one of which is a typical lymphatic leukemia and one a myelogenous leukemia:

Lymphatic Leukemia.—No. 13,597. Leslie J., aged nine years, entered the hospital in April, 1917, one week before his death. His family history was not obtained, since he entered alone, having been sent from another city. All we could obtain was that he was one of a family of six living children and one brother had died. He himself had had most of the childhood diseases. One year ago had had measles and since then had never been normal. Four months before he entered the hospital the glands of his neck became enlarged. He received at that time some *x*-ray treatments which he said caused the glands to go down for about two and one-half months when they began swelling again. On the left side of his neck one of the glands had become semi-fluctuant. This time he had fever and one of the glands had been opened but he said there was no pus only a bloody discharge. Two weeks before he entered the hospital his loss of strength became more marked. He was brought in by a social worker from a distant city. Physical examination showed a pale poorly nourished boy who held his head forward in a peculiar manner. His voice sounds were nasal and slurred. His breath was foul. Tongue was coated, the nasopharynx and mouth were covered with ulcerated areas which were coated over with a putrid fibrinous membrane which was clinically not diphtheritic. There was a good deal of bloody discharge from the nose and mouth which was very foul and troublesome. The lymph-nodes of all the superficial glands were enlarged, discrete, and firm. The chest showed very few abnormal signs. The *x*-ray picture of the chest indicated that there was a beginning pressure on the right apex. This could not be made out clinically because both sides of the lungs were filled with bubbling râles. The heart signs were of poor quality but without a definite murmur. The liver was greatly enlarged extending down 10 cm. in the right nipple line below the costal margin. The spleen extended 9 cm. below the costal margin. It was firm. There were no other abdominal masses felt. Laboratory findings gave no indication of lues or diphtheritic infec-

E. S., Aged, Four or Five Years. Period of Observation September, 1919, to January, 1921

Date	Hb.	Red blood-cells	White blood-cells	Poly. N	S.M.	L.M.	Tr.	Eos.	Bas.	Platelets	Remarks
Sept. 11...	70	4,160,000	55,600	9	82	5	..	4			
Sept. 16...	74	4,928,000	82,000	4	61	30	..	5	...	.....	1 megaloblast
Sept. 19..	84	4,730,000	61,400	6½	82½	11	..	1			
Nov. 22...	80	5,200,000	12,400	32⅔	51	9	..	6⅔	⅔		
Nov. 29...	..	.....	10,800	32	51	10	..	7	...	213,200	
Dec. 16...	83	4,700,000	11,200	52	43	3	..	2			
Dec. 22...	80	5,270,000	12,600	41	45	9	..	5			
1920											
Jan. 6....	85	5,864,000	7,400	55	25	6	4	5			
Jan. 10...	91	4,880,000	15,700	49	10	22	..	12	...	220,000	
Jan. 16...	89	4,680,000	14,250	32	22	23	..	12	2		
Jan. 21...	..	4,944,000	17,000	37	48	6	..	7	2		
Jan. 30...	93	4,588,000	19,600	35	19	21	..	2	1	208,000	
Mar. 20....	71	4,688,000	13,000	56	28	7	..	7	...	118,000	
Apr. 21,..	97	5,004,000	18,200	49	5	16	..	9	...	130,000	
Apr. 28...	85	4,404,000	17,600	62	11	13	..	1	1	84,000	
May 6....	73	4,734,000	13,500	37	39	22	..	2			
May 17...	70	4,825,000	10,400	28	43½	19½	..	8½	½		
July 14...	80	5,100,000	11,600	58	36	5	..	1			
Sept. 23...	81	4,760,000	11,800	53	33	7	2	3	...	194,000	
1921											
Jan. 15...	70	4,864,000	12,040	46	43	7	3	2	1	240,000	

tion. The von Pirquet was negative. The throat gave a culture of non-hemolytic streptococcus. The blood picture as given here shows the typical secondary anemia with marked increase at first in the white cells, practically all being small lymphocytes. After a few days there was a sudden drop in the white count, falling from 69,000 to 2400 within a period of 48 hours. A transfusion was given at this time but did not produce any results whatever. His white count fell on the day of his death to 600. The only cells that could be seen in the smear were small lymphocytes. No other cells could be made out.

Blood Picture

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Small lymphocytes	Large mononuclears and transitionals	Myelocytes
Mar. 29.....	70	3,456,000	74,000	3	0	0	96	1	0
Mar. 31.....	..	.....	69,000	2	1	1	65	30	1
Apr. 2.....	..	.....	2,400	5	0	0	84	10	1
Apr. 3.....	..	3,600,000	2,000		only lym	phatic	seen		
Apr. 4.....	45	2,810,000	600		only lym	phatic	seen		

Autopsy showed a beginning aspiration pneumonia and caseous tubercular nodules of the bronchial lymph glands. The heart showed a few petechial hemorrhages on the visceral pericardium and a few hemorrhages beneath the endocardium of the left ventricle. The spleen was large, firm and on section showed a uniform consistency with some increase in connective tissue and of a reddish pink color.

It was difficult to make out the Malpighian bodies. The liver was also large, firm and of a reddish color, and the centers of the lobules stood out as yellowish green foci. Microscopically throughout all the organs there was diffuse infiltration with small round lymphoid cells. The cervical gland, axillary, inguinal, most of the glands of the chest, the bronchial and intestinal glands, as well as the liver, spleen and kidney showed this same infiltration. The bone marrow which was very red, soft and cellular was almost entirely composed of small round lymphoid cells.

Myelogenous Leukemia.—June, 1915, No. 9304, John B., aged six months, remained in the hospital for five weeks before his death. There was history of tuberculosis in the family, but of no blood disease. He was the only child. *Past history.* He had never been well, having cried continuously since birth, more at night than in day-time. In spite of that he appeared to his parents to be in good condition until he was four months of age. He had had several intestinal upsets and his parents thought that his stools had always been soft and greenish and occasionally had mucus and some blood. At seven weeks of age he had been covered with a rash which had been diagnosed as eczema. From the fourth month on he had ceased to gain in weight. At this time he began to lose strength rapidly and for the first time an abdominal tumor was noticed, four days before he entered the hospital.

Physical examination showed a child very emaciated, pale, with prominent veins below the costal margin. There were petechial areas scattered all over the body. The lymph-nodes could be observed from a distance. Cervical, axillary and inguinal glands were all enlarged. The heart and lungs were negative. The abdomen was much extended; the liver extending 6 cm. below the costal margin was firm. The spleen reached to a point 1 cm. to the right of the umbilicus and was palpable as a firm pear-shaped mass 16.5 cm. long and 10 cm. wide, the upper border being 8.5 cm. below the nipple in the nipple line. Wassermann and von Pirquet reactions were negative. The appearance of anemia, paleness, purpuric areas, all increased during his stay in hospital. Continuously lost weight and became steadily weaker. His blood picture as given here shows the characteristic increase in the myelocytes, the presence of basophils and nucleated red cells in large number. One curious and unusual finding was the high red blood-cell count throughout and no time had it gone down to normal count notwithstanding the fact that the hemoglobin dropped from 80 per cent. to 45 per cent. at one time. There was marked achromia and definite change in the size and shape of the red cells, poikilocytosis and anisocytosis. No staining was done for reticulation and none of the newer vital tests were used nor Graham's oxydase test attempted. His platelet count, however, was followed as was his coagulation time. We found that his platelets were increased, the highest being the count of June 1 when the platelets numbered 1,120,000. They never went below 200,000. The coagulation time done at room temperature by removing blood from the jugular vein, put into a test tube 15 mm. diameter, 2 c.c., 13 minutes. A control done under the same conditions was 12 minutes. His prothrombin did not show any variation from normal, the re-clotting time being, with two drops of $\frac{5}{10}$ per cent. calcium solution, two and six-tenths minutes, and with three drops nine minutes.

His autopsy gave a diagnosis of acute myelogenous leukemia, hyperplasia of spleen. Acute pleuritis. Subpleural hemorrhages. Hemorrhage into left lung. Hemorrhage into left pleural cavity. Hyperplasia, mesenteric lymph-nodes and retroperitoneal lymph-nodes. Peyer's patches, and solitary lymph follicles of intestines. Multiple hemorrhages of liver, stomach, intestines, kidneys, spleen. Multiple small erosions of the stomach. Hemorrhages, subpial, of the brain. The spleen weighed 230 gm. and measured 14.5 by 8.5 by 5 cm. The liver weighed 500 gm. The bone marrow was very soft, dark, reddish brown in color. The glands on section were soft, uniform pale grayish interior with small reddish hemorrhagic areas scattered throughout. Microscopic examination showed throughout all the organs, in blood-vessels and capillaries, large numbers of fairly large round cells, some with dark staining nuclei. The spleen section showed slight thickening of the capsule. The sinuses were dilated. The interstitial tissue

seemed uniformly increased. There was evidence of hyperplasia of the germinal centers. Dilated vessels contained many mononuclear cells and some red cells. The eosinophils were scattered through the section. The liver showed the same predominance of large mononuclear cells profusely scattered throughout. The same large mononuclears were found in the kidney, adrenals and all the lymph-nodes. These large mononuclear cells belong definitely to the myeloid series.

ANEMIA INFANTUM PSEUDOLEUKEMIA (VON JAKSCH)

This condition was first mentioned by Gretzel in 1867, though it is not until 1889 that the first clear, clinical description of the condition was reported by von Jaksch. Von Jaksch considered the condition an entity but came to the conclusion that it was necessary to differentiate what he considered a true case of "anemia infantum pseudoleukemia" from the secondary anemias arising after such a condition as rickets. He differentiated the "anemia infantum leukemia" from other conditions with leukocytosis in several ways. In "anemia infantum pseudoleukemia," eosinophilia is either absent altogether, or very slight, whereas the red blood-cell count and the hemoglobin may be found much lower than in most leukemias. Von Jaksch also called attention to the fact that in "anemia infantum pseudoleukemia," the liver is only slightly enlarged, whereas in the true leukemias the liver is very much enlarged. Anemia infantum pseudoleukemia is characterized, according to von Jaksch, by an oligocythemia, oligochromasia with a leukocytosis which is rather high and continuous, with a spleen which is markedly enlarged, with a liver enlargement slight or only moderate and with a favorable prognosis. Since von Jaksch's paper first appeared, many cases of splenic anemia have been reported and up to the present time there has been no unanimity of opinion as to whether the condition is secondary to congenital lues or rickets or is a primary condition. Among most American writers the feeling is that the condition is a secondary anemia with a relatively distinct clinical picture. Many British writers feel that it is a distinct disease, or at least speak of it as such. Many of the German writers are divided—some feeling that it is a secondary anemia peculiar to children, others that it is a primary condition, an entity in itself. Ostrowski* is of this opinion whereas Carr† holds the opposite view, though Carr admits that lues or rickets may occur with or even predispose to this type of splenic anemia in children. Carr claims that in the great majority of children with rickets there is no enlargement of the spleen at any time and that there is no connection, where the two exist together, between the severity of the rickets, the size of the spleen or the amount of anemia, and that in some cases of anemia there are no signs of rickets.

From present data concerning the etiology of the condition we feel that it is probably a reaction to some type of infection; the infecting organism may not in all cases be the same but the effect on the blood-forming organs *is* the same. This type of reaction occurs more

* Ostrowski, S., Jahrb. f. Kinderh, Berlin, lxxiii, n.F. (1911), pp. 690–703.
† Carr, Lancet, London (1892), p. 907.

BLOOD PICTURE

Date	Hb., per cent.	Red cells	White cells	Differential count; nomenclature, Pappenheim; stain, Wright's							
				Poly-morphs	Myelo-cytes	Lympho-cytes	Lymph-oids	Eosino-phils	Baso-phils	Nucle-ated reds	Large mononu-clears
May 27	75	7,860,000	61,900	20.0	25.0	15.0	17	2.0	6.0	14.0	0
May 30	80	.....	57,300	38.5	20.5	11.5	5	11.5	8.5	9.5	0
June 2	..	.....	66,200	18.5	15.0	20.0	4	4.5	8.0	28.0	
June 5	75	7,384,000	47,800	30.0	30.0	10.0	3	1.0	9.0	16.0	2
June 13	75	7,264,000	95,000	13.0	16.0	15.0	0	4.0	7.0	40.0	3
June 16	50	5,944,000	103,200	12.0	20.0	16.0	0	2.0	5.0	45.0	2
June 21	45	6,022,000	112,000	27.0	27.0	10.0	1	0.5	2.5	30.0	3
June 25	50	6,580,000	112,000	15.0	7.5	14.0	..	...	2.0	60.0	
June 28	50	6,752,000	120,000	20.0	22.0	6.0	2	0.0	7.0	42.0	
June 30	50	6,096,000	112,000	25.0	15.0	6.0	2	1.0	3.0	48.0	1
July 2	60	6,040,000	176,000	9.0	13.0	13.0	14	2.0	1.0	47.0	1
July 2	..	.....	316,000								

Died one hour after last count.

often in children who have had nutritional disturbances such as have led to rickets, or where they have had the parental handicap of lues or tuberculosis. For in both these conditions we find a certain number of cases which develop the characteristic syndrome which is known as von Jaksch's anemia. The reaction in these cases comes very close to the type of reaction found in splenomedullary leukemia. It is undoubtedly a reaction of lesser intensity than that occurring in what we have come to consider primary leukemias and certainly the prognosis is far more favorable. With this point of view Gordon Ward* would agree. He advances the name of "secondary infective myelemia of infancy," or possibly "rachitic myelemia." Ward thinks that the condition is a hyperplastic process of the lymphatic tissue, similar in essentials to that seen in leukemia but starting on a lower grade. He thinks that the blood changes do not give rise to the marked leukocytosis of leukemia, nor are the abnormal cells found in such large numbers, but when they are found they are identical with those found in leukemia. He thinks that this idea of the condition harmonizes all the chief anomalies recorded from time to time and that it explains the post-mortem findings and the blood picture. He thinks the enlargement of the spleen fits in with the infective theory as also does the enlargement of the glands, and the blood picture is an evidence of the lower level of hyperactivity of marrow and spleen than in the case of primary leukemias, so that the output of abnormal cells is less and the interference with the output of normal cells is correspondingly less. Ward's view of von Jaksch's disease is as follows: "The disease is a reaction of the infantile blood-forming organs to infection. The actual infecting organ is not known nor necessarily specific. The particular reaction is only produced when rickets is present and it is probable that the conditions present in rickets are in some way responsible for the reaction taking the form which it does. There are therefore two essential etiological factors of which neither alone would prove sufficient—*viz.*, infection as an exciting factor and rickets as a predisposing factor."

The condition is found in children more often between the ages of six months and two years, the majority being in the second half of the first year. The analysis of reported cases shows a slight predominance in males. It is interesting to note that twins have frequently been affected and Hutchinson† believes that Jewish children are quite susceptible. American figures do not bear this out.

Pathology.—The spleen is markedly enlarged; it may fill the whole left half of the abdomen; it is hard and firm and there is considerable overgrowth of the fibrous tissue, and the Malpighian follicles have more or less completely disappeared. Occasionally there is some evidence of a perisplenitis. The liver is enlarged in about 50 per cent. of the cases and there is a slight increase in the connective tissue which gives the liver a firm hard appearance. The liver cells are not changed.

* Ward, G., Brit. Jour. Chil. Dis., xv (1918)

† Hutchinson, Allbutt and Rolleston, "System of Medicine," v, p. 782.

The superficial lymph glands of the cervical, inguinal and axillary regions may be moderately enlarged though their involvement is by no means constant. These glands do not show any marked change in their structure and represent a moderate hyperplasia. The bone marrow is usually active, and has a red appearance, though in severe cases there is a megaloblastic proliferation. The blood changes show quite a reduction in the red cells. In severe cases, the red cells may fall as low as a million and a half though the usual count is between two and three million. The hemoglobin is usually proportionately reduced. The color index is generally low, ranging between 0.6 and 0.8 though in some cases the color index may be above 1. The size of the red cells varies considerably so that anisocytosis and polychromasia may be quite marked. Poikilocytosis is not a marked feature, nucleated red cells may be very abundant, often reaching as many as 2000 per cm. Megaloblasts, cells with fragmented nuclei, and mitotic figures are sometimes seen. Neither their appearance nor the number of nucleated red cells bear any relation to the severity of the disease. There is usually only a moderate leukocytosis, varying between 20,000 and 40,000. The white cells are often difficult to place. They are apparently intermediate in form between lymphocytes and polymorphonuclear cells. A large number of them may be called transitional. The lymphocytes predominate, averaging about 50 per cent., though they may be as high as 70 per cent. Transitional cells average about 12 per cent. Polymorphonuclear cells average about 30 per cent. The eosinophils usually average less than 5 per cent. Myelocytes are usually found. Cowie* has described a large mononuclear cell which is sometimes granular and with a protoplasm which stains pale blue. Marrow cells as described by Stillman† are also seen; "the nuclei of this cell (marrow cell) shows a structure which is considered typical of the megaloblastic nucleus, while the cytoplasm is intensely polychromatophilic having a peculiar slaty blue color." The blood platelets are increased.

Symptoms.—The symptoms usually develop slowly. The pallor is marked; the face often appears puffy and waxy; a greenish tint has been described. The children are usually apathetic. They do not complain of pain; often run a slightly irregular temperature, and there is often a history of some gastro-enteric disturbance. Upon examination, the abdomen is found enlarged; the spleen sometimes fills more than half the abdomen, the spleen is not tender but hard and firm. Ascites is occasionally present. The liver can usually be felt but is not markedly enlarged. The glandular system may or may not be enlarged. The glands are usually small and hard. The examination of the blood makes a diagnosis fairly certain though in severe cases the blood picture may have to be followed for several weeks before one feels certain that the condition is not one of the primary anemias.

* Cowie, Phys. and Surg., Detroit and Ann Arbor, xxxi (1909), pp. 541–544.

† Stillman, R. G., A Study of von Jaksch's disease, Am. Jour. Med. Sc., cliii (1917), p. 218.

Petechial hemorrhages have been found in severe cases. The condition tends to pass through a rather slow cycle—the onset usually consumes several months before the condition has reached its height; then the condition remains stationary and under favorable treatment recovery is slow but steady. Improvement in the blood picture, diminution in the size of the spleen, and general nutritional improvement progress simultaneously. The number of red cells and hemoglobin returns slowly to normal as the white cells diminish.

Treatment.—Arsenic, in the form of Fowler's solution, has given the best results. In infants, it is better to give doses of one or two drops four or five times a day, rather than large doses less frequently. Iron, in combination with arsenic, has a useful place in treatment. It may be given as the saccharated carbonate or citrate of iron. The hypodermic use of iron gives better results, especially in those cases in which there are gastro-enteric symptoms of vomiting and diarrhea. In such cases the intravenous use of neosalvarsan gives very good results, in minute doses, 0.01, 0.02 or 0.03 gm. depending upon the age of the child. There is no question that radium has a very profound effect on the size of the spleen. We believe, however, that the use of *x*-ray or radium should not be undertaken unless the child is under the most careful and constant supervision.

General hygienic and dietetic treatment is most important. Careful regulation of the food, introducing those foods which have been found to have the greatest effect upon the blood-forming organs, such as scraped meat and spinach, gives the best results. Fresh air and rest, conserving the child's strength as much as possible are important factors in the recovery.

The prognosis should not be bad in the ordinary case. These children, however, but poorly withstand secondary infections and those with parenteral diseases, such as lues or tuberculosis, more especially those under one year of age, usually end fatally. In the uncomplicated cases complete recovery usually takes from two to three months.

The following history is fairly typical of this type of anemia:

Hospital No. 6761. V. N., aged eight months. Family history negative except for the fact that the mother had had one miscarriage and for the fact that the mother had had osteomyelitis of her lower jaw during this pregnancy. The child, however, was full term and weighed 6½ lb. at birth. She had never been nursed and her feeding history was one of many changes. She had been on practically every proprietary food known. From birth she had apparently had a yellow waxen color. Her physical examination on entering showed a very pale infant with a face adenoid in type and of a pasty yellow color. Her mucous membranes were pale and slightly cyanotic. Lymph-nodes of the neck were palpable. The tonsils were enlarged. The epiphyses were enlarged with a definite rosary. The head, however, did not show any marked squaring or bossing. The heart was enlarged and there was a definite hemic murmur. The abdomen was distended. The spleen could be felt 7 cm. below the left costal margin in the nipple line. The liver was enlarged to a point 4 cm. below the costal margin. The blood picture was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Jan. 10.....	10	1,375,000	10,600	45.0	4.5	0	45.5	5.0
Jan. 13.....	15	1,400,000	9,800	43.0	1.0	0	53.0	3.0
Jan. 15.....	15	1,264,000	10,200	42.0	2.0	0	45.0	11.0
Jan. 20.....	15	2,216,000	10,400	44.0	1.0	..	43.0	12.0
Jan. 25.....	20	2,151,000	7,300	42.0	2.0	..	51.0	5.0
Jan. 29.....	20	2,320,000	.....	44.0	1.0	0	50.0	5.0
Feb. 8.....	20	1,868,000	9,000	49.0	...	0	42.0	8.5
Feb. 10.....	10	1,480,000	13,000	37.5	0.5	0	56.5	6.0
Feb. 15.....	15	1,940,000	11,800	63.0	...	0	21.0	14.0
Feb. 18.....	15	1,824,000	12,400	62.0	...	0	31.0	7.0

There was marked poikilocytosis and anisocytosis; normoblasts were always present and two or three were found in counting 200 cells. The patient received injections of citrate of iron every other day amounting to a grain of iron. Her diet was carefully regulated and when discharged she was improved slightly. Her history after discharge was of slow but definite improvement. Within six months after discharge she was practically well. Her blood picture was normal, her spleen was still slightly palpable and the lymph-nodes had gone down to almost normal though they could still be felt.

SPLENIC ENLARGEMENT IN INFANCY AND CHILDHOOD, DUE DEFINITELY TO SECONDARY CAUSES

The spleen during infancy and childhood is often enlarged under other conditions than those connected with diseases of the blood-forming organs, and sharply separated, of course, from enlargement of myelogenous leukemia which, however, rarely occurs during infancy and childhood.

The spleen, according to Kaufman, weighs 9 gm. at birth; according to Holt,* at birth the spleen weighs 7.7 gm.; at 3 months, 15.5 gm.; at 12 months, 23.2 gm.; at 2 years, 38.5 gm.; and at 3 years, 46.4 gm. An enlarged spleen always shows some degree of lateral movability. Its surface is usually smooth and superficial, being easily felt just below the abdominal wall. The sharp edge is broken by one or more characteristic notches. As the spleen enlarges it extends downward and obliquely to the right but maintains the general shape of a normal spleen. The spleen may be found enlarged due to circulatory disturbance either from congenital or acquired cardiac conditions. In the former it usually takes on a chronic enlargement without any tenderness, whereas in acquired cardiac diseases it is usually associated with some perisplenitis and may be quite tender on palpation. It is usually not hard unless the cardiac condition is of long standing and a chronic enlargement results, though this is not the rule. Associated with this is always an enlargement of the liver which usually comes first and is due to disturbance in the

* "Diseases of Infancy and Childhood."

portal circulation. The spleen enlarges usually secondarily and to a much less extent. It is also found enlarged in chronic pulmonary conditions, such as emphysema, and in interstitial pulmonary infections, though the enlargement in these conditions is usually not great. The spleen can often be felt from 1 to 2 cm. below the costal margin. The spleen is often enlarged in certain acute infections particularly in malaria and typhoid. In malarial districts associated with acute or chronic malarial infections, the spleen may become very large and extend down almost to the umbilicus, if not below. This condition, however, is becoming rare even in what used to be malarial regions and as malaria is more and more controlled this type of splenic enlargement will become less in this country. During typhoid the spleen is acutely enlarged though it usually does not extend more than 2 or 3 cm. below the costal margin. It is soft and at times tender. It is associated with more or less perisplenitis. In many acute infections other than these an enlargement of the spleen is often found due to acute congestion and to acute syphilis. It responds almost as readily to acute infections during infancy and childhood as do the lymphatic glands and it usually subsides with great rapidity with the clearing up of the infection. Thus it is found enlarged in most of the acute exanthemata, though it is often overlooked. It is found markedly enlarged in acute miliary tuberculosis and in general chronic tuberculosis of infancy and childhood. In tuberculosis it may reach as far as the umbilicus, though usually the enlargement is less than this, being from 2 to 3 cm. below the costal margin. It is usually firm and not tender though in very acute miliary tuberculosis there may be some perisplenitis together with the acute splenitis. In the chronic infections and intoxications with metabolic disturbances such as rickets it is the rule to find the spleen somewhat enlarged though only to a moderate degree. In congenital lues due to the diffuse fibroid change with or without formation of gummata, the spleen is found enlarged. It may be the only sign of late lues in which case it is at times associated with occasional attacks of jaundice. The following case illustrates some of the difficulties that may arise in making a diagnosis in luetic splenomegalies:

Hospital No. 5322. F. F., aged four years. The father had a positive Wassermann reaction, otherwise the family history was negative. She had resided in China and Hawaii for eight months. *Past History.* She had never been sick, always been a well child from infancy until the present illness. The present illness began shortly after her return from the islands, when it was noticed that she was somewhat pale and listless. She did not complain of any pain and she had no temperature and her splenomegaly was only found on examination. Physical examination showed a small, fairly well developed, excitable child. Pallor of the skin and conjunctivæ was marked. No abnormalities were detected by physical examination except those of the liver and spleen. The liver was 5 cm. below costal margin, hard and firm and edge could be easily felt. The spleen was 5 cm. below the costal border in the nipple line. It was hard, firm, smooth and freely movable. Her von Pirquet, Widal, and blood examination for malaria and her blood cultures were all negative. Her Wassermann was also negative. Her blood examination

showed a rather interesting leukopenia with an absolute lymphocytosis. During her stay in the hospital she developed acute tonsillitis with temperature. This was accompanied as shown in the record of her blood between Dec. 11 and 15 by increased white cell production. However, even with this increase there was no increase in the proportion of polymorphonuclears. While in the hospital examination of her stools showed on two occasions occult blood and during this same period two superficial hemorrhagic areas appeared on her lower extremities. Her blood picture was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Dec. 8.....	80	3,846,000	4,800	23	0	0	63	14
Dec. 11.....	80	4,253,000	13,000	20	0	0	49	31
Dec. 12.....	..	.....	29,000	17	0	0	57	26
Dec. 15.....	80	4,757,000	19,000	22	0	0	62	56
Dec. 20.....	85	4,352,000	6,400	17	0	1	33	49
Dec. 30.....	80	4,160,000	3,400	36	0	0	26	38

Her platelets varied from 150,000 to 300,000, being at the lower limit during the period when blood was found in her stools and the hemorrhagic areas noted on her extremities. The red blood-cells showed pallor, some poikilocytosis and anisocytosis. The large lymphocytes which were definitely increased belonged to the lymphoid series. On anti-luetic treatment over a period of several months her blood picture entirely cleared up and her spleen returned to normal.

The following case illustrates enlargement of the spleen due to acute streptococcus infection:

Hospital No. 13,293. L. O., aged seven weeks. She was the third child of healthy parents. She had been delivered instrumentally after labor lasting 34 hours. She was only breast fed for three days when the mother developed a fever. She was then put on to a modified milk mixture on which she had done very well. Her weight had decreased since birth until at the time of her entry into the hospital it was only $8\frac{3}{4}$ lb. At three weeks of age a swelling was noticed in her right thigh in the region of Scarpa's triangle. The only abnormality on physical examination was the enlarged liver which was felt 1 cm. below the costal margin in the nipple line. The spleen was palpable 3 cm. below the costal margin, and her right leg was swollen and rotated outward, flexed at the hip and knee. The tissues of the groin were swollen. The tumor mass was 6 cm. in diameter. The entire right leg was nearly half as large again as the left leg. The tumor mass was tender, red and firm; deep fluctuations could be madeout; *x*-ray showed only the soft tissues of the thigh to be involved. Pirquet and Wassermann were negative. The abscess was opened and the culture showed long chain-like hemolytic streptococci. Her blood picture was as follows:

Date	Hb., per cent.	Red cells	White cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Large mononuclears and transitionals
Feb. 12.....	75	3,584,000	28,900	73	1	0	21	3
Feb. 15.....	..	.....	41,300	89	1	1	6	3
Feb. 16.....	..	.....	45,000	86	1	0	8	5
Feb. 17.....	..	.....	38,700	84	0	0	15	1
Feb. 21.....	..	2,576,000	23,900	73	0	0	25	2
Feb. 24.....	..	.....	18,800	62	1	2	30	5
Mar. 6.....	..	.....	9,000	47	0	0	48	5
Mar. 23.....	80	4,000,000	7,800	43	1	0	48	8

The secondary anemia was a feature of the case. It is interesting to note that the anemia was pronounced four days after the operation, but on discharge the hemoglobin, the red cells and the white cells had returned almost to normal. On appropriate diet her general condition improved rapidly.

Talbot* has reported a case of "kala-azar" in a child—the first American case. In this condition the spleen may become enormous, filling the abdomen. It is usually associated with pain and tenderness. The condition can be diagnosed by a splenomegaly, and mononuclear cells with the Leishman-Donovan bodies can be found in great numbers. In Talbot's case the liver was found 4.5 cm. below the costal margin, and the spleen was from 3 to 4.5 cm. below the costal margin and 3 cm. to the right of the umbilicus. The notch was easily felt. The blood picture showed a low platelet count. The blood had at times a more marked leukopenia, both of which, as Talbot remarks, suggested an aplastic anemia. Splenectomy was performed on this child and the spleen was found to weigh 330 gm. Leishman infantum bodies were found in the spleen. Leishman-Donovan bodies were recovered from the inguinal glands by culture. Following her splenectomy she improved for a short time but subsequently began to lose weight and strength rapidly. She was then given intravenous injection of tartar emetic, 1 c.c. of a 2 per cent. solution daily at first and then every other day. After a month of treatment the temperature which she had been running subsided. She was discharged after two months from the hospital apparently well and was seen a year later when she was apparently well. This is the only case reported in this country. The disease is common in India and on the coasts of the Mediterranean, and may come to this country at any time from these regions. The parasite was first described by Leishman-Donovan in 1903. It is supposed to be transmitted from dogs to man, possibly by fleas. The onset is insidious though it may commence with chills and fever, the fever being either of the intermittent or remittent type. The fever usually lasts for six weeks or longer and then declines. During the period of temperature the spleen and liver become enlarged, the anemia

* Talbot, F. B., Am. Jour. Dis. Child., xvi (1918), p. 156.

increases and there is marked loss of weight. Death usually occurs within a year. Treatment in these cases has been unsatisfactory. The treatment used by Talbot was suggested by Sir Leonard Rogers.*

In these true secondary splenomegalies, the treatment should of course be directed to the primary cause. When this is removed the spleen usually reduces to normal, and there is no need of treatment for the anemia beyond the general lines laid down for the treatment of secondary anemia—rest, hygiene and diet. Prognosis, of course, depends upon the primary cause and varies from that of the acute infections or chronic metabolic disturbances, in which it is usually good, to that of tuberculosis in which the primary disease usually ends fatally.

* Rogers, Lancet, London (Nov. 4, 1916), and Indian Med. Gazette, lii (July and Aug., 1917).

CHAPTER LXXVIII

HEMORRHAGIC DISEASES

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GENERAL CONSIDERATION OF HEMORRHAGIC DISEASES

With our present knowlege of bio-chemical and bio-physical properties of the blood we can attempt a general discussion of the various factors that enter into most of the true hemorrhagic diseases. The general principle of coagulation and the factors that enter into this have been discussed in a preliminary chapter. It is from these studies that it is now at all possible to make a clear-cut etiological classification of hemorrhagic diseases. It is not always possible, but still an attempt to make such a classification will materially assist in our understanding of these conditions and will certainly make our treatment more rational. Not all the factors that enter into normal coagulation, as stated, are clearly understood, but it is possible to group the diseases with abnormalities in their coagulation, and to study all these various factors that are deranged. Hurwitz* has lately made a very good attempt at classifying the various hemorrhagic diseases on this plan.

1. Platelet Group of Diseases.—There can be no doubt that a diminution in the platelets is responsible for certain types of bleeding. As already pointed out, purpura hemorrhagica belongs to this type. It was discussed in connection with the aplastic anemias because, as Minot has pointed out, there is undoubtedly a pathological aplasia of the megacaryocytes and an absolute diminution of the platelets. The reduction of platelets in certain types of chronic purpura has been pointed out by Duke.† Blood platelets have a mechanical rôle, as shown by Duke, in their glutinability, as well as in their production of prothrombin or cytozyms, which, in combination with serozym and calcium unites to form prothrombin. Platelets play a very intimate part in the coagulation of the blood and when they are decreased in number, or when their prothrombin element is either lacking or diminished, delayed coagulation time results. The prolonged bleeding time and non-retractility of the clot which is a characteristic of purpura hemorrhagica is, as was pointed out, dependent directly upon this platelet deficiency.

* Hurwitz, S. H., Amer. Jour. Med. Sc., cliv (1917), p. 689.

† Duke, W. W., Jour. Amer. Med. Assn., lv (1910), p. 1191; Arch. Int. Med., xi (1913), p. 100; Jour. Am. Med. Assn., lxv (1915), p. 1600.

THE DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC DISEASES BASED UPON A STUDY OF THE BLOOD

Hemorrhagic diseases	Coagulation time	Bleeding time	Number of platelets	Retractility of clot	Factors of coagulation				Fibrinolysis	Remarks
					Prothrombin	Antithrombin	Fibrinogen	Calcium		
I. Primary hemorrhagic disease:										
(*A*) Hemophilia	Prolonged	Normal	Normal	Normal	Diminished	Relatively increased	Normal	Normal	Negative	Demonstration of prothrombin deficiency is a reliable *in vitro* test for the diagnosis of the hemophiliac condition.
(*B*) Morbus maculosus neonatorum.	Prolonged	Normal	.....	Normal	Diminished	Normal	Normal	Normal		
(*C*) Purpura hemorrhagica	Normal	Prolonged	Markedly diminished	Non-retractility of clot	Normal	Normal	Normal	.....	.....	Diminution in number of platelets and non-retractility of clot make diagnosis of purpura possible, even in absence of other features.
(*D*) Chronic purpura	Normal	May be prolonged	Diminished	Non-retractility of clot	Normal	Normal or increased	Normal	.....	Negative	
II. Secondary hemorrhagic disease:										
1. Blood diseases	Prolonged	Prolonged	Diminished	Diminished	Diminished	Normal or increased	Normal	.....	.....	Coagulation time and bleeding time both prolonged (compare with hemophilia).
(*A*) Aplastic anemia										
(*B*) Leukemia	May be prolonged	Normal or prolonged	Normal or diminished	Normal or diminished	Normal	Increased	Slightly diminished	.....	Negative or positive	Platelets diminished in lymphatic leukemia; increased in myeloid leukemia; fibrinolysis present in myeloid; absent in lymphatic leukemia.

2. Hepatic disease.....	Normal	Prolonged	Normal	Normal	Normal	Normal	Diminished	Normal	Positive	The prolonged bleeding time in cirrhosis with hemorrhatic symptoms is due to the fibrinogen deficiency; the clot is too soft to close the ruptured vessels.
(*A*) Cirrhosis of liver	Normal or prolonged	Normal	Normal	Normal	Normal	Normal	Normal	Diminished	.....	Blood calcium may be present in excess but it is bound by bile pigment and is unavailable for prothrombin activation.
(*B*) Cholemia obstructive (without liver injury).	Prolonged	Normal or prolonged	.....	.....	Normal or diminished	Increased	Normal or diminished	Normal	May be positive	Terminal drop in prothrombin noted in one instance; prothrombin may be diminished in congenital family jaundice and in congenital stenosis of bile ducts.
(*C*) Cholemia (with liver injury).	Normal or prolonged	Normal or prolonged	Normal or slightly diminished	Normal	Normal or diminished	Increased	Normal or diminished	Normal	.....	Bleeding time prolonged in chloroform poisoning due to fibrinogen deficiency; platelet count may be diminshed during acute stage of infections; prolonged coagulation time and bleeding in septicemia due to anti-thrombin excess.
3. Infections and intoxications (symptomatic purpura): septicemia, typhoid, tuberculosis, chloroform poisoning.										

NOTE.—Above table taken from "Etiology and Treatment of Hemorrhagic Diseases, S. H. Hurwitz, M.D., Amer. Jour. of Med. Sciences, New Series, cliv (1917), p. 689.

2. Prothrombin Group.—The prothrombin factor or the cytozym is deficient under hemophiliac conditions. This group includes not only those with a definite family history of hemophilia but also those cases which develop hemophilia without any previous history of this condition having been inherited, and in certain hemorrhages of the newborn which have been described by Whipple.* We have found the same lack of prothrombin in certain cases of melena neonatorum. Whipple† has brought forward certain evidence that goes to show that in such cases prothrombin may be present at birth, but vanishes for some unknown reason during the first few days of life. At least the power to produce prothrombin from cytozym must be lacking for a short period, and this accounts probably for the success which follows intravenous injection of whole blood in such cases, tiding over the period of depressed prothrombin production. In aplastic anemia, as already stated, there is a marked diminution if not an almost total absence of platelets, along with the failure of the bone marrow to produce red blood-cells and granular leukocytes. The same condition of defective marrow occurs in benzol poisoning and in over-stimulation of the marrow by Roentgen rays or radium.

3. Fibrinogen and Fibrinolytic Group.—The fibrinogen factor is most often affected in association with liver injury. This has been demonstrated in such poisons as chloroform and phosphorus.‡ In conditions where the liver is injured the blood coagulates but the clot is flabby. The same conditions may occur in cirrhosis of the liver. In certain disturbances of the liver a fibrin ferment has been demonstrated. This occurs especially in hepatic cirrhosis with insufficiency and is also present in certain cases of myeloid leukemia.

4. Calcium Group.—Calcium is probably never absent to such a degree that bleeding is caused by an absolute lack of calcium but rather to the fact that calcium is bound up with the bile pigments, especially in cases of obstructive jaundice. The test for calcium *in vitro* can be used to prove whether calcium is deficient or whether some other factor is at fault. If we follow Howell's theory and accept the presence of anti-thrombin this element may be present in excessive amounts under certain hemophiliac conditions such as certain chronic purpuras with increased bleeding time and non-retractility of the clot. These, however, may be attributable to the lack of cytozym in the platelets or to their diminution in the blood. However, other factors have been shown to be at fault at times, such as fibrinogen.

5. Anti-thrombin and Thromboplastic Substances.—The presence of anti-thrombin is usually associated with liver injury and such a condition usually arises in acute intoxications or infections which affect the liver, producing liver injury with icterus. Certain investigators have assumed that in hemophiliac conditions there is a

* Whipple, G. H., Arch. Int. Med., ix (1912), p. 365.

† Whipple, G. H., and Moss, W. L., Forchheimer's "Therapeusis of Int. Dis." D. Appleton and Co., New York, v (1915), p. 802.

‡ Whipple, G. H., and Hurwitz, S. H., Jour. Exper. Med., xiii (1911), p. 136.

deficiency in thromboplastic substances. This substance is difficult to determine outside of its presence in the platelets and tissue juices. For the present, at least, it may be assumed that an examination and study of platelets both numerically and as to their cytozym content will explain conditions in which there is supposed to be a deficiency of thromboplastic substance.

HEMORRHAGIC DISEASES OF THE NEWBORN

Hemorrhagic disease of the newborn is a term which covers a condition found in infants which occurs usually within the first few days after birth. The term includes many conditions due to disturbance of various factors in the coagulation of the blood. It may be due to sepsis or may be a sign of syphilis. It may be due to liver disturbance with the fibrinogen factor deranged. It may be due to a disturbance in the platelets or prothrombin. The condition is evidenced by persistent oozing, usually from several surfaces. It may be slight or very pronounced. The true type of hemorrhagic disease of the newborn, which is not secondary to any definite disease or condition, is usually self-limited and either ends fatally within a few days or is checked, either by itself or by appropriate treatment.

The etiology of this disease has presented many difficulties. Mauriceau (quoted by Lovegren) mentioned this disease in 1682, but did not assign for it any cause. Since then many cases have been reported, with an etiology for every presentation. Lovegren* in reviewing the subject suggests the theory of gangrene of the intestine, which was first brought forward by von Siebold. Bulard also in 1828 attributed it to intestinal ulcerations. Effusions of blood into the esophagus and lesions in the mucosa of the intestinal tract were demonstrated by von Chrzanowski† and Fuhrman, and Schloppler* have described punctiform hemorrhages throughout the digestive canal. Unger has attributed it to acute hemorrhagic enteritis. Graham‡ in 1912 reviewed all the hemorrhagico-icteric conditions of the newborn including Buhl's disease, Winckel's disease, icterus neonatorum, hemorrhagic disease of the newborn, etc., and mentions Cruveilhier's findings in 1827 of gastric ulcers and states that this is the accepted idea of most modern observers. Graham divides the etiologic conditions, excluding true hemophilia, into five types—syphilis, infections, mechanical factors, heredity and known chemical agents. The theory of infection is supported by the writings of such men as Knopfelmacher, Heubner, Runge, Bendix, Hutinel, Merklin, Holt, etc. Graham himself considers the factor as asphyxia or chloroform poisoning, the underlying condition being a deficiency of oxidation of a general or local character existing in all of these states associated with hemorrhage or icterus or both. Somewhat along these

* Lovegren, Jahr. für Kinderh., lxxviii (1913), p. 249.
† Jahr. für Kinderh., lxxviii (1913), p. 249.
‡ Graham, Jour. Exp. Med., xv (1912), p. 307.

lines was the theory of Ebstein-Oesterr* who believed the cessation of respiration at birth with resulting asphyxia caused a great increase of vascular tension and the possibility of extravasation and ulceration of the stomach. Many such hypotheses have been advanced. Hyperemia of the intestinal vessels, erosion with perforation, thrombosis of the umbilical vein due to asphyxia, blocking of the ductus Botalli with a thrombosis, hemorrhagic infarcts in the floor of the fourth ventricle, widespread fatty degeneration, have all been held accountable for these hemorrhagic conditions in the newborn. Stamm† in his report gives an autopsy finding of anemia of all the organs, subdural and subpleural, ecchymosis and a necrotic ulcer of the duodenum. Simmonds‡ in four cases found respectively umbilical sepsis, atresia of the duodenum, a congenital heart lesion and multiple hemorrhagic erosions of the intestines. Local changes in the capillaries have been thought to be the cause by Frankel§ and Vorpahl.‖ This resembles somewhat one of the findings suggested by Hess in hemophilia. Soresi (quoted by Schloss) presupposes a metabolic change both in the blood and blood-vessels. Ballard¶ considers the etiological factors to be either mechanical or infectious, and considers the essential factor to be dyscrasia of the blood constituents themselves. Syphilis without doubt plays a part and an important one in certain cases. Schloss** reports two cases with a luetic history and Krosing†† has reported another case with a definite luetic history. In Whipple's‡‡ case the father was luetic and Lespinasse and Fisher§§ ascribe lues as the cause for from 2 to 6 per cent. of the cases. Wassermann reactions from newborn infants are consistently negative even in flagrant cases and it is therefore only possible to ascertain a luetic infection by testing the blood of the parents. Even where there are no clinical symptoms or where lues has not been suspected in the family a Wassermann may very clearly demonstrate the connection between lues and this condition. There is no question that in certain cases there is a relationship between lues and hemorrhagic disease of the newborn.

Sepsis may also cause multiple hemorrhages. Practically every known organism has been found. The clinical picture, however, of true hemorrhagic disease of the newborn is not one of sepsis. The possibility of intra-uterine infection is brought forward by Commandeur‖‖ and Turck¶¶ demonstrated in some experiments on animals,

* Jahr. für Ped. (1876), p. 7.
† Stamm, Münch. Med. Wochen., lxi (1914), p. 1947.
‡ Simmonds, Münch. Med. Wochen., lxi (1914), p. 1947.
§ Frankel, Münch. Med. Wochen., lxi (1914), p. 1947.
‖ Vorpahl, Arch. für. Gyn., xcvi (1912), p. 377.
¶ Ballard, Bull. Soc. Obst. et de Gyn., iii (1914), p. 508.
** Schloss, Amer. Jour. Dis. Child., i (1911), p. 276.
†† Krosing, Münch. Med. Jour., lxix (1912), p. 280.
‡‡ Whipple, Arch. Int. Med., xii (1916), p. 637.
§§ Lespinasse and Fisher, Surg. Gyn. and Obst., xii (1911), p. 40.
‖‖ Commandeur, Bull. Soc. Obst. et de Gyn., i (1912), p. 297.
¶¶ Turck, quoted by Hymanson, Arch. of Ped., xxix (1912), p. 761.

by feeding B. coli to pregnant animals, the possibility of causing hemorrhages, premature births and even death.

In the case of sepsis, as pointed out by Whipple,* the anti-thrombin factor is often increased. This theory of infection then adds another hypothesis as to the cause of hemorrhagic disease of the newborn.

The literature does not say very much about heredity as being a possible factor. It is mentioned by Graham,† and Pitfield‡ has reported a family in which four infants in succession showed icterus with hemorrhages, two of them dying. Reichard§ has reported a case in which a brother had died at the age of four days of gastro-intestinal hemorrhage. Lues was not present in either case. Swain, Jackson and Murphy (quoted by Lespinasse and Fisher) report a family history in which the paternal grandmother had died of pernicious anemia and a cousin had died of melena at the age of four days. In Jenning's‖ case also the mother died of pernicious anemia shortly after the birth of the child. Bonnet-Laborderie¶ has advanced an interesting hypothesis based on repeated examinations of the mother's milk in a case of hemorrhagic disease. He found a toxic irritative substance in the mother's milk which caused changes in the gastric mucosa. There was increased hyperemia of the gastric and intestinal mucous membrane with an exaggeration of the peristalsis and active anti-peristalsis which produced vomiting and bleeding.

In 1911 the first attempt to find a definite etiologic factor in the blood itself was undertaken by Schloss and Commiskey.** They examined the coagulation time but found very unconstant results. Lespinasse and Fisher†† report the findings of Carrel, Lambert and Brewer who made the first transfusion in a case of hemorrhage of the newborn. They thought because of the rapid recovery that infection or change in the capillaries could not be an adequate explanation and suggested that the condition must be due "to a change in the chemical condition of the blood." "The solution of the problem of its etiology is to be found in a chemical study of the process of osmosis in capillary vessels, of the chemistry of the coagulation of the blood and along kindred lines which are for the most part new and untouched." Schwartz and Ottenburg (quoted by Lespinasse and Fisher) conclude from their study that impaired blood coagulation is at the basis of the disease and that it is most probably due to an interference in the production of thrombokinase. In 1912 Schloss and Commiskey‡‡ again reviewed their cases. In one case they found a poor clot which seemed to indicate a deficiency in fibrinogen. All the factors for

* Whipple, Arch. Int. Med., ix (1912), p. 365.
† Graham, Jour. Exp. Med., xv (1912), p. 307.
‡ Pitfield, Arch. of Ped., xxix (1912), p. 761.
§ Reichard, Jour. Amer. Med. Assoc., lix (1912), p. 1539.
‖ Jennings, Jour. Amer. Med. Assoc., lx (1913), p. 1154.
¶ Bonnet-Laborderie, Bull. Soc. Obst. et de Gyn., xvi (1913), p. 630.
** Schloss and Commiskey, Am. Jour. Dis. Child., i (1911), p. 276.
†† Lespinasse and Fisher, Surg., Gyn. and Obst., xii (1911), p. 40.
‡‡ Schloss and Commiskey, Am. Jour. Dis. Child., iii (1912), p. 216.

coagulation were present because spontaneous clotting occurred. The coagulation itself, however, was incomplete, the clot being very easily disintegrated. They gave experimental proof for the presence in adequate amounts of thrombin and calcium, the thrombin, in fact, being actually in excess. Their findings are as follows: In four cases the coagulation time was normal, in two cases slightly delayed, in two cases distinctly delayed and in two cases absent or greatly delayed. "In certain cases not explainable by deficiency or absence of thrombin or fibrinogen, however, in other words, with normal coagulation of the blood, the condition seems to be due to some local vascular lesion or defect present only in the bleeding areas." Later Schloss* reports a case with deficiency in thrombin and another with deficiency in fibrinogen. Lovegren† ascribes the condition to faulty coagulation. Richards‡ in a study of cases eliminated fibrinogen from consideration as a causative factor because the quantity supplied in a small amount of serum administered therapeutically would not be sufficient to cause permanent clotting. He says: "The fault must be in the thrombokinase, salts or prothrombin. Thrombokinase may be disregarded since it comes from the tissue juices and none was allowed to contaminate the serum used. Calcium is of no value therapeutically and is ruled out on that basis." He therefore decided that the fault lay in the prothrombin deficiency due to a low platelet production. In his case the platelet count during the bleeding time was 20,000 per c.c. rising slowing to 347,000 per c.c. after the bleeding stopped. Whipple's§ observations on different types of bleeding including icterus, anemias, hepatic disease, etc., showed in all but one the presence of an excess of antithrombin. In that one, which was a case of hemorrhagic disease of the newborn, there was a very marked deficiency and almost absence of prothrombin.

Many English writers have called the condition "hemophilia of the newborn" and in certain cases there is close resemblance between the blood changes, though in true hemophilia the platelets are not diminished but the available prothrombin is diminished, so that there is a prothrombin deficiency in both conditions but with a widely different course. In hemorrhage of the newborn there is a spontaneous arresting, or, on occasion, a rapid progression to a fatal termination. In hemophilia there is a chronic condition, the organism being unable to establish a normal prothrombin level in the blood if this is tested from time to time, the tendency to bleeding always being present, whereas in hemorrhage of the newborn, once the child has recovered the tendency has passed.

Gelston‖ has lately been able to study a case of hemorrhage of newborn which showed a distinct lack of prothrombin. During the

* Schloss, Am. Jour. of Obst., lxvii (1913), p. 820.

† Lovegren, Jahr. für Kinderh., lxxix (1914), p. 708.

‡ Richards, Med. Record, lxxxi (1912), p. 69.

§ Whipple, Arch. Int. Med., xii (1913), p. 637.

‖ "Etiology of Hemorrhagic Disease of the Newborn," Am. J. Dis. Child, xxii (1921) p. 351.

period of hemorrhage and eight hours after the cessation of hemorrhage prothrombin was present in normal amounts. These findings corroborate those of Whipple and show in addition to loss of prothrombin-anti-thrombin balance its most remarkable re-establishment.

Etiology.—Etiologic studies of tissue from hemorrhagic disease of newborn have given very little that bears on the cause of the disease. Usually very little or nothing is found at the time of autopsy. The areas from which the hemorrhage occurs may often be difficult to determine. Often sero-hemorrhagic exudates are found from all the mucous membranes, especially of the gastro-intestinal tract, skin, pericardium, pleura, peritoneum and even from the brain and spinal cord. Extravasations of blood within the organism may be extensive. As we already noted, ulcers have probably been the most frequent definite pathologic lesion mentioned, but what the origin of the ulcers may be is not known. In 1914 Green* pointed out that in hemorrhagic disease of the newborn, intarcranial hemorrhages are not infrequent and that these are associated with hemorrhage into other serous cavities as well as general ecchymosis of the skin. Warwick† reports that intracranial hemorrhages were found in 50 per cent. of stillborn infants or those who died in the first few days. Out of 18 infants in whom hemorrhages were found, eight had hemorrhages in other organs than the brain. The coagulation time of the blood was delayed in five of the cases. The occurrence of hemorrhagic disease of the newborn varies according to statistics from 1 to 4 per cent. Green and Swift‡ found it in 1.14 per cent. whereas Holt found it in between 3 and 4 per cent.

General Symptoms.—In most cases there is spontaneous bleeding which occurs during the first week of life, rarely after the twelfth day. Hemorrhages are usually multiple and may occur in any part of the body. Ritter in a study of 190 cases found that the bleeding was from the umbilicus alone in 97 cases, and from the umbilicus associated with bleeding in other parts of the body in 138 cases, from the intestines in 39 cases, from the mouth in 28 cases, from the stomach in 20 cases, from the conjunctivæ in 20 cases, from the ears in 9 cases. Townsend in 50 cases found bleeding from the intestines in 20 cases, subcutaneous ecchymosis in 21 cases, stomach in 14 cases, mouth in 14 cases, nose in 12 cases, meninges in 4 cases, umbilicus in 18 cases, 3 of these being from the umbilicus alone, cephalhematoma in 3 cases, abdomen in 2 cases, abrasions of skin in 1 case and from the pleura, lungs and thymus in 1 case each. The most frequent cases are of bleeding from the umbilicus, then from the intestines, then from the stomach, and lastly from the brain. The amount of hemorrhage is not usually great but there is continual oozing so that unless the hemorrhage is checked the total amount of blood lost may be considerable.

* Green, R. M., Boston Med. and Surg. Journal, clxxi (1914), p. 715.

† Warwick, M., Amer. Jour. Med. Sc. (1919), p. 95.

‡ Green, R. M., and Swift, J. B., Boston Med. and Surg. Jour., clxiv (1911), pp. 454–56.

In all cases there is a rapid loss of weight and marked prostration. This is often noted early in the disease before much blood has been lost. The temperature is variable. Green finds the temperature high in comparatively few of his cases in the Massachusetts Lying in Hospital. He found a subnormal temperature more often than a normal or high temperature. The temperature, however, may be either high, subnormal or low. In cases in which it tends to be high the appearance of diarrhea is not an uncommon symptom.

Umbilical Hemorrhage.—There are three types of hemorrhage noticed from the umbilicus: (1) From the arteries alone. This may be attributed to the lack of physiological cessation of circulation in the umbilical arteries. (2) From the lumen of the umbilical vessels at the level of the umbilicus. This is characterized by oozing and usually occurs within the first days of life. Hemorrhage of this type is fairly rare. (3) Parenchymatous umbilical hemorrhages, which are the most frequent. The umbilical vessels are closed and blood oozes from the capillaries at the base of the navel. Grandidier claims that only 17 per cent. of these children recover. However, with modern methods of treatment this should be distinctly reduced.

Hemorrhage oftentimes occurs into other organs of the body. Umbilical hemorrhages tend to occur later than those from other parts of the body, often not appearing until the fourth and sometimes appearing as late as the seventh day.

Intestinal and Stomach Hemorrhages (Melena Neonatorum).—The name "melena neonatorum" is not applied to any disease as an entity, it means simply the loss of blood from the gastro-intestinal tract, either by vomiting or by rectum or both. According to Vidal* there are three varieties of melena neonatorum—melena spuria, melena vera and melena symptomatica.

Spurious melena designates the loss of blood from the gastro-intestinal tract when the hemorrhage does not really originate there. Blood from the gastro-intestinal tract due to epistaxis, pulmonary hemorrhage or the bleeding nipples in the nursing mother comes under this name. Mills† emphasizes the frequency of mistaken diagnosis because of the bleeding of the mother's nipples. *Symptomatic melena* is the presence of blood in the gastro-intestinal tract when this hemorrhage is only one symptom of a general demonstrable disease. *True melena* is the hemorrhage dominating the entire disease picture. Hemorrhage from the gastro-intestinal tract usually comes on within the first four days of life. Hematemesis and bloody stools may cease after a single occurrence and the child may show no further signs. In other cases the child dies from loss of blood with the picture of hemorrhagic shock. The bleeding may last for a few hours or days. Silberman has estimated that the average mortality of these cases is 44 per cent.

Hemorrhage from the Mouth and Nose.—Hemorrhages of any great quantity rarely occur from the mouth or nose. So-called hem-

* Vidal, P., Thèses de Paris (1911–2).

† Mills, H. B., Am. Jour. Obstr., lxxii (Dec., 1915), p. 1067.

orrhages from the mouth and nose may really be from the pharynx, esophagus, stomach or bronchial hemorrhages. The bleeding in the mouth may be associated with ulceration of the hard palate from thrush or fissures of the lips. Hemorrhages of the nose are due more often to syphilis than any other cause. Such hemorrhages are repeated but not continuous or profuse.

Meningeal Hemorrhages.—Most authors agree that meningeal hemorrhages in most instances are due to trauma in an overwhelming percentage of cases, though where it is associated with hemorrhages from other parts of the body, meningeal hemorrhages are probably due to some factor of disturbed coagulation which has caused the general hemorrhage.

Hemorrhage from the Conjunctivæ.—Hemorrhage from the conjunctivæ is rarely found even associated with conjunctivitis.

Hemorrhage from the Female Genitals.—Hemorrhage from the genitals is not an uncommon finding from the third to the sixth day, but the bleeding, as far as we have been able to observe, never disturbs the well being of the child, when it occurs from the genitals alone. When it is associated with general bleeding the outcome is very serious.

Hematuria.—When the urine is stained with blood it may be a sign of hemorrhage from the urethra, bladder or ureter or kidney. It may be with or without symptoms elsewhere. It is often very severe and ends fatally. Very slight bleeding occurs occasionally from uric acid infarcts.

Prognosis.—The prognosis depends upon the extent of the hemorrhage as to what type of treatment is instituted. Slight hemorrhages tend to recover spontaneously. Severe hemorrhages have a mortality between 50 and 60 per cent. Green and Swift* give a mortality of 60 per cent. for cases of umbilical hemorrhage; 50 per cent. for those who have sero-mucous hemorrhage; and 22 per cent. for those who only show purpuric lesions. Most cases that have hemorrhage from the meninges, or rare cases that have hemorrhage into the thymus or adrenals, succumb.

Treatment.—With the introduction of transfusion with either citrated blood or with whole blood, using the paraffin syringe method, the mortality of hemorrhagic disease of the newborn has been greatly reduced. It is probably life-saving in all cases except those due to sepsis or those connected with syphilis. Where syphilitic symptoms occur early hemorrhage is protracted and usually fatal. In congenital syphilis where bleeding occurs early infants usually die from the general syphilitic infection rather than from the amount of blood lost and transfusion in these cases does little good. Active prophylaxis during the prenatal period has undoubtedly diminished the number of such cases during the past decade and active treatment begun at the time of birth may have some effect on those born with syphilitic manifestations. Before the introduction of transfusion many therapeutic measures

* Green, R. M., and Swift, J. B., Boston Med. and Surg. Jour., clxiv (1911), pp. 454–6.

were recommended such as calcium, gelatin, adrenalin, and styptics of all types. None of these has any effect and in our experience they are worthless. Serum was used very extensively before the present methods of indirect transfusion became popularized. Serum unless it is fresh diminishes in its thrombin quantity and increases in its antithrombin quantity so that unless serum is fresh it is not indicated but rather contra-indicated. However, many successful cases have been reported and in former years we have had success with the use of fresh human or animal serum. We see no reason for using it at the present time, however. Whole blood may be introduced either subcutaneously or intravenously. In mild hemorrhages a subcutaneous injection of from 10 to 25 c.c. of blood from the mother will often be sufficient to check the hemorrhage. On the other hand it is comparatively easy to inject whole blood directly into the sinus of newborn infants and this in our opinion is the method to choose, using a Goldbloom block and needle and a 20 to 50 c.c. Luer syringe coated with paraffin. The blood from a grade 4 donor should be introduced. However, because of the fact that a very small percentage of newborn infants have any definite grouping, less than 16 per cent., as already (Happ) mentioned, mother's blood or any available blood may be used with little chance of injury or serious reactions. As mentioned before, at birth very few infants have either isohemaglutins or isohemolysins. This indirect transfusion not only supplies the necessary factors for coagulation but where there has been any considerable loss of blood it also replaces the red blood-cells and serum. Where it is found difficult or inadvisable to use the paraffin syringe or paraffin covered tubes and needles as suggested by Vincent,* citrated blood may be used made up as already described. Instead of using the large flask, as only from 50 to 150 c.c. of blood should be introduced at any one time, it is easier to use a large syringe, and if possible two such syringes will make the procedure very simple. As far as our experience goes, only two conditions occur under which the longitudinal sinus cannot be entered, one of hematoma placed over the region of the sinus and the second where there has been so much molding of the head that the sinus cannot be found. In our experimental work we have found at times difficulty where there is marked over-riding in entering the sinus, but if one is experienced with the general location, even if there is over-riding to a considerable extent, one can usually make out where the sinus should be though the ordinary landmarks in such conditions are lacking. Since Helmholtz† first suggested this route we have used it in preference to any other for all types of intravenous injection (except neosalvarsan).

Results of Transfusion.—Since the introduction of methods of transfusion the mortality of hemorrhagic disease of the newborn, except in the case of sepsis or syphilis, has been reduced very greatly.

* Arch. Ped., xxix (1912), p. 887, and Boston Med. and Surg. Jour., clxvi (1912), p 627

† Amer. Jour. Dis. Child., ii (1915), p. 194.

Lespinasse* reported a mortality of 8.1 per cent. and Green† a mortality of 10 per cent. If the transfusion is done early the mortality should practically be nil and as this is being recognized we believe the mortality will gradually approach zero except in sepsis and lues.

The following case illustrates not only the etiology of the diminished prothrombin content but also the value of intravenous injection of citrated blood:

No. 10898. A baby boy born full term, normal delivery. There was no family history of tuberculosis but Wassermann reaction in the father was positive. There was no hemorrhagic tendency in the family. At 48 hours after birth oozing was noticed from the base of the cord. At first local applications of cephalin were tried over the bleeding area but the oozing continued. At the end of this period the child showed slight pallor. A slight subconjunctival hemorrhage appeared in the right eye and blood was noted in the stools.

Blood Examination.—The first blood count made eight hours after hemorrhage began showed hemoglobin 75 per cent., red blood-cells 3,488,000, white cells 14,000 with a differential count of 43 per cent. neutrophils, 1 per cent. eosinophils, 42 per cent. small lymphocytes, 14 per cent. large lymphocytes, two normoblasts. The platelet count was 435,000. The clotting time at this time of whole blood taken from the longitudinal sinus was 70 minutes, the prothrombin time 105 minutes, anti-thrombin content normal, and fibrinogen normal. The boy then received three injections of citrated whole blood, 10 c.c. given into the buttocks, and in all 50 c.c. into the longitudinal sinus. The bleeding stopped within half an hour. The blood count eight hours after the hemorrhage was checked showed a hemoglobin of 40 per cent., red blood-cells 1,968,000, white count 24,600; differential count, 75 per cent. polymorphonuclears, 6 per cent. small lymphocytes, 13 per cent. large mononuclears and transition cells, one normoblast; anisocytosis and poikilocytosis were marked. At this time the blood platelets showed 385,000, whole blood clotting time 18 minutes, prothrombin time normal, that is, 10 to 12 minutes. Three days later the hemoglobin showed 50 per cent., red blood-cells 2,704,000, white blood-cells 20,000; differential count, polymorphonuclears 57 per cent., small lymphocytes 22 per cent., large mononuclears and transitionals 21 per cent., and the blood platelets were 385,000.

This case illustrates, as pointed out by Gelston who made the study on the blood, a definite etiological factor at fault, namely the prothrombin, and it also illustrates the efficacy of indirect transfusion done early.

PURPURA

Symptomatic and Idiopathic Purpura

We have already described the blood condition in which, due to the deficiency of platelets, hemorrhage appears. This condition, as stated, is true purpura hemorrhagica and should not be confused with the type of purpura here discussed. In true purpura hemorrhagica there is a definite diminution in the blood platelets. In symptomatic purpura, on the other hand, there is no diminution of platelets. In certain forms of idiopathic purpura there might be a moderate diminution though it never reaches the low point found in purpura hemorrhagica. As a rule counts are above 100,000.

This type of purpura has received many names. From the fact that the name itself means a cutaneous hemorrhage dermatologists

* Lespinasse, V. D., J. A. M. A., lxii (1914), p. 1866.

† Green, R. M., Boston Med. and Surg. Jour., clxxi (1914), p. 715.

have vied among themselves to give every peculiar distribution of hemorrhage some particular name, and if it is combined with erythema or with urticaria or with angioneurotic edema some of the commoner names are purpura simplex, purpura rheumatica, Henoch's purpura, Schonlein's purpura, purpura erythema nodosum, purpura urticaria pigmentosa, and so forth.

Osler has grouped many of these conditions into a fairly definite clinical entity, placing them in the erythema group, either with visceral complications or lesions, or exudative manifesations. If one has seen many cases of this type of purpura one has been struck by the multiform type of eruption, sometimes the more evident being as a hemorrhage, sometimes as hemorrhage and erythema and sometimes the hemorrhage being located quite deeply in the tissue, sometimes superficially connected with blebs or nodules or with edema of the angioneurotic type. It must be clear to anyone studying this type of allied conditions that there is no sharp line of differentiation. Cases that at first appear to be purely superficial may at a different time in the course of the disease have joint symptoms or again visceral symptoms. From the symptom which predominates the disease usually gets its name, either purpura simplex, purpura rheumatica, Henoch's purpura, or visceral purpura.

Purpura may also occur as a part of some other disease. Thus it is common to find purpura connected with the acute infective diseases, particularly eruptive fevers. It is not uncommon to see purpuric lesions during the course of measles or scarlet fever or during acute diphtheria. Usually it is a sign of very severe infection, so much so that the popular term of "black measles" or "black diphtheria" has been gained from this symptom. Purpura is also sometimes found associated with acute or chronic tuberculosis.

Purpura is either widespread, when it is a secondary or symptomatic manifestation, or it may be localized to the extremities. In acute malignant endocarditis, purpuric areas may appear due to bacterial emboli, or during acute intoxications, non-bacterial, in eruptions such as drug eruptions. We have just had an opportunity of seeing such a one accompanied with angioneurotic edema and purpura covering the whole body following a neosalvarsan injection. It may appear while giving iodin or arsenic. It may also appear following injection of antitoxic sera, in which case, as in some of the other conditions, it would appear to be a type of anaphylaxis. Whether it is this or whether, due to the permeability of the blood-vessel, hemorrhage occurs, is not known.

In certain metabolic conditions in infants not only hemorrhagic skin symptoms appear, but also an angioneurotic condition which undoubtedly has something to do with the salt metabolism, and is undoubtedly a disturbance of the sodium and calcium balance. This has experimentally been proved by Chiari and Januscke* who were

* Chiari, R., and Januscke, H., Wien Klin. Wchnsche., xxiii, No. 4 (1910), p. 27.

able to produce pleural effusions by intravenous injection of sodium iodid into dogs and to prevent this if at the same time they injected calcium chlorid. Minot and Lee* mention having been able to obtain serohemorrhagic effusions into the skin in a similar manner by injecting sodium iodid and preventing it by calcium.

Diagnosis.—It is not difficult to diagnose this type of symptomatic purpura because it is usually a part of some other infection, or occurs during an administration of a drug or antitoxin. There is nothing very regular about the lesions. They may be either diffuse or local. The lesions are confined to the skin and are not found in the mucous membranes as they are in purpura hemorrhagica, and they are also more likely to be deeply placed. There is little tendency to bleeding as the platelets are not diminished, though in septic conditions bleeding from the mucous membranes may be present at the same time that purpura appears on the skin. This we have seen frequently in cases of infectious diarrhea, in general septicemia, as mentioned in the hemorrhagic types of the dangerous eruptive diseases, in septic endocarditis and septic nephritis.

The blood shows little change. There is no deviation from normal in coagulation time, bleeding time and retractility of the clot. In fibrinolysis at times there may be a secondary anemia associated with the primary disease as well as a leukocytosis.

Treatment.—This should be directed towards the primary disease, the purpura itself needs no treatment.

Purpura Rheumatica.—This type of idiopathic purpura is very prone to occur in children. It is a simple purpura with joint involvement. At times in chronic types it may affect the joints causing hypertrophic changes somewhat similar to those found in hemophilia. There is usually more than one joint involved, and not uncommonly it is associated with edema and urticaria and erythema. It is very likely to recur. It is often confused with rheumatic fever as with it is associated at times a temperature and sore throat. The temperature, however, is not very high, usually running between 38 and 39°C. The joints may be quite swollen, filled with fluid, and painful; when associated with urticaria and erythema it may easily be mistaken for rheumatic fever. There is no involvement of the endocardium, however, and the symptoms usually last for only a few days. The salicylates have little or no effect. The joints are often tender and pain may be a marked symptom. The joint symptoms usually precede the appearance of purpura though this is not always the case. Where endocarditis accompanies the arthritic and purpuric symptoms we should feel that the condition was probably a rheumatic fever infection and not a purpura rheumatica. The purpura is usually general though it appears first on the legs, then on the arms, then on the trunk.

Henoch's purpura, or **visceral purpura,** is characterized by the purpura on the skin plus certain visceral symptoms, particularly

* Nelson Loose Leaf Medicine, p. 128. Vol. IV ch. 3, p, 128.

intestinal and kidney. There may be definite cramp-like pains in the abdomen, followed by bloody discharges, or there may be definite renal colic with bloody urine. The abdominal condition often occurs first followed by the purpuric eruption. It may be associated with edema and urticaria. In this type of purpura there may be a slight temperature and the condition has a tendency to recur. Sometimes the symptoms follow each other in succession, though they may all appear at the same time. Occasionally joint symptoms may occur simultaneously or they may precede or follow the visceral symptoms so that the two types of purpura, that is, purpura rheumatica and visceral purpura, may be combined, which is the reason for thinking that they have probably the same etiology. The renal symptoms and visceral symptoms are due to rapid exudation of serum into the intestinal walls or into the kidneys. Wherever this effusion is there will be local tenderness and distention. If it occurs around the iliocecal valve it will resemble appendicitis. It is often so severe, especially where there is evacuation of blood following such a colic, that it will resemble an acute intussusception and is often mistaken for this, though intussusception occurs normally in infants, whereas this condition rarely occurs in infants under two years of age and is very much more likely to occur to older children and young adults where intussusception is rare. Intussusception is never accompanied by purpuric eruptions, and the sausage shaped mass of intussusception is lacking. Vomiting often occurs during the acute colic and at times blood is found in the gastric contents. When the kidneys are involved the whole onset may resemble that of an acute nephritis. The presence of blood, pain, temperature, and at times marked impairment of kidney function, all resemble an acute nephritis. There is usually more tenderness over the kidney in Henoch's purpura than in the ordinary type of acute nephritis because of the edema and swelling that occurs in the kidney. This is usually associated with hemorrhagic purpuric eruptions and may be associated with arthritic manifestations, though erythema is present. These conditions have been very well described by Sir William Osler, beginning with his publication in 1895 when he first grouped these conditions of visceral complications as "Erythema exudavium multiformæ"* up to one of his late articles in the British Medical Journal i (1914) p. 517, "The Visceral Lesions of Purpura and Allied Conditions."

The duration of these single attacks either of arthritic or visceral manifestations is usually only two or three days but there is a very marked tendency for them to recur so that the duration of a single attack may cover a period of weeks.

There have been few blood analyses during these attacks. Edsall† has reported an increased protein metabolism. The blood picture in these cases is usually very little changed. The coagulation time may be slightly increased though this is not a characteristic

* Am. Jour. Med. Sc., cx (1895), p. 629.

† Edsall, D. L., Am. Jour. Amer. Sc., cxxx (1905), p. 589.

feature. The platelets may be diminished though not so low as to be considered the cause of bleeding, in fact they may be increased and the coagulation time decreased, as in the following case of simple idiopathic purpura:

Hospital No. 931. N. K., 11 years old. His family history is unimportant. He had had measles and pertussis in early childhood. At the age of nine had had a severe fracture of the pelvis. At 10 a fracture and dislocation of right elbow. He had had his tonsils removed 10 months before the present illness which began 10 days before he entered the hospital with an acute pharyngitis. Two days before entering the hospital large purpuric areas had appeared on both legs. Physical examination was negative, except for the skin condition. His legs showed slight edema and on both lower extremities, scattered irregularly, were from 16 to 18 purpuric areas measuring from 1 to 2 cm. in diameter. The same type of purpuric areas was found on the thighs and dorsal surface of right arm. Slight amount of tenderness was evidenced over the purpuric areas. His temperature ranged from 36.6 to 38.4°C. His blood Wassermann was negative and blood cultures were negative. His blood chemistry showed no increase in non-protein nitrogen urea, uric acid or creatinin. His throat culture showed a pure culture of staphylococcus aureus. His blood picture showed hemoglobin ranging from 80 to 90 per cent., red blood-cells 4,320,000 and a white count that varied between 6400 and 12,600. His differential was normal. His platelets ranged from 315,000 to 330,000 and his coagulation time from five to six minutes, with blood taken from vein in the elbow. Prothrombin time was normal and retractility of clot normal and there was no fibrinolysis.

As has been stated, at times these cases of idiopathic purpura have a marked tendency to be chronic. Some cases have more or less continuous symptoms of purpura for long periods. As the disease takes on this chronic aspect there is usually a definite change in the blood picture. They show signs of a secondary anemia of the type found in chronic hemorrhage, that is, a low hemoglobin, reduced red blood-cell count and tendency to slightly elevated leukocytic count, with increase in polymorphonuclears and a reduction in platelets, though not to anything like the extent found in purpura hemorrhagica.

Elsner and Mead* have reported a case with a considerable decrease in the platelets. Such a case would resemble very closely idiopathic purpura hemorrhagica. In such chronic cases bleeding from the mucous membranes may be present, especially epistaxis. In such cases, however, careful blood studies should be carried out and it is our opinion that most of these cases, which at first sight may be thought to be idiopathic purpura, will really turn out to be true cases of purpura hemorrhagica. Though these cases may continue for long periods the tendency is to recover. When death does occur it is more often associated with extreme visceral complications or with hemorrhages into the brain or subdural hemorrhages.

Apparently there is no form of treatment outside the general regimen which should be laid down, of limited activity, avoidance of infections and appropriate diet. In other words, keeping up the general well-being of the child and preventing infection rather than in direct treatment for the purpura.

* Elsner, H. L., and Mead, F. M., Am. Jour. Med. Sc., cxlv (1913), p. 178.

There is a type of purpura, which is very acute, termed "purpura fulminans." This is a type that occurs in children under 10 years of age, runs a very acute and stormy course and often ends fatally in from 18 hours to three or four days. Elliott* has lately summarized such a case.

Mixed Type of Purpura.—Hospital No. 22,220. C. K., aged two years and seven months. Family history negative. Child was full term child and had had no diseases up to present time. Feeding history had been uneventful. Three days before the child entered the hospital he started vomiting. He came into the hospital with acute abdominal pain, vomiting and passing some thin bloody mucus. At the time he was taken with the vomiting it was noticed that there was swelling of the left leg which was painful at the ankle, and also the elbow on left side was swollen. The next day his right instep became swollen and then the right elbow, and then in succession both knees. He was in a great deal of pain. Temperature ranged from 37.6 to 38.2°C. His physical examination showed nothing except the swellings, and purpuric spots varying from the size of a pin-head to that of a small pea were found on both legs and both wrists on the flexor surfaces. There was very little abdominal tenderness. The hemorrhagic spots on the legs were rather deeply placed and surrounded by blueness of the skin. Later on he had eruptions on both arms. The joint swellings disappeared as the purpuric spots became more evident. His colic and bleeding disappeared within 24 hours after entering the hospital. Blood examination showed hemoglobin 75 per cent.; red blood-cells 4,090,000; white cells, 17,000. Differentials, 53 per cent, polymorphonuclears, 27 per cent, small lymphocytes, 19 per cent, large mononuclears and transition cells, 1 per cent. eosinophils. His platelet count was 200,000. Coagulation time 12 minutes. Bleeding time four minutes. Retraction of clot complete in 20 hours and firm. No fibrinolysis. Four days after entrance all the purpuric areas had disappeared. His pain and colic completely cleared up and temperature was normal. This case illustrates a combination of simple purpura, purpura rheumatica and Henoch's purpura or visceral purpura.

Purpura Simplex.—Case 235, F. L., aged three and one-half years. Family history negative. Past history was not obtained as he was brought in by a district nurse, who gave a history of his present illness that a week before black and blue marks had appeared on his legs. Next day there was a blue mark noticed on his chin. These marks spread covering his thorax and back. The night before entrance he had epistaxis which lasted for over an hour. On the morning of his entrance he had a second attack of epistaxis which lasted only a few minutes. His physical examination showed a healthy child and was essentially negative except for the purpuric eruption. There were small areas of ecchymosis over the left ankle and leg and on the right leg; rather larger areas on the axillary region and back and a few areas on his face. There were one or two purpuric areas on his scalp just adjacent to his ears. His blood picture showed a hemoglobin of 70 per cent., red blood count 4,700,000, white count 16,200. Differential, 76 per cent, neutrophils, 20 per cent. small lymphocytes, 4 per cent. mononuclear and transitionals and 1 per cent. eosinophils. His platelets varied from 190,000 to 290,000. His coagulation time was eight minutes. Bleeding time two and one-half minutes. His temperature ranged from 37 to 38°C. He was in the hospital for eight days at the end of which time he was completely well. There had been no spots for the last five days.

HEMOPHILIA

Hemophilia may be defined as an hereditary condition characterized by a tendency to hemorrhage, which appears only in males, transmitted only by females who have inherited the condition. The blood shows a constant deficiency of prothrombin with delayed coagu-

* Elliott, E. A., Arch. Int. Med., iii (1909), p. 193.

SUMMARY OF BLOOD EXAMINATIONS

Case	Date	Hydrogen-ion conc. P H*	Coagulation time, minutes		Retractility of clot	Fibrinolysis	Platelets (thromboplastin)	Prothrombin			Anti-thrombin			Fibrinogen in gm. per 100 c.c.	Treatment
			Patient	Control				Patient	Control	Quotient	Patient	Control	Quotient		
Case 1, G. R.	6/11	....	335	32	+	0	352,000	76	8	9.5	44	40	1.1	.....	Ten cubic centimeters whole blood given subcutaneously June 5, and 20 c.c. June 6. Kephalin 5 c.c. (0.05 gm.) subcutaneously on July 1, 4 and 7. Elevation of temperature to 40°C. and local reaction. Kephalin 0.1 gm. doses daily from August 1 to August 25.
	9/12	7.8	195	15	+	0	.....	180+	7	25.0+	36	40	0.9	.....	
	10/18	....	23	16	++	0	296,000	57	10	5.7	40	47	0.8	0.494	
	11/10	7.75	240	19	+	0	.....	...	..	....	...	...	...	.....	
	12/15	....	220	30	+	0	.....	160	17	9.4	61	82	0.8	.....	
Case 2, J. McC.	10/8	....	40	16	+	0	580,000 (Oct. 12)	60	14	4.3	28	20	1.4	.....	October 7 and 8 wound packed with sterile cotton soaked in 2.5 per cent. sterile kephalin and firm pressure applied. Twelve intramuscular injections of 5 c.c. kephalin (2.5 per cent. sterile solution) from October 7 to 15, and nine intramuscular injections of 5 c.c. kephalin (1 per cent. in 6 per cent. glucose solution) from October 16 to 27. December 1 to 4 and 8 to 11 inclusive, exposure of tibiæ and femora to Roentgen rays. Dose, 5 milliampere minutes.
	10/18	7.65	240	19	++	0	.....	195	10	19.0	37	47	0.8	0.420	
	10/21	....	...	..	+	...	192,000	...	..	....	...	...	...	.....	
	10/28	....	180	30	+	0	.....	90	19	4.7	63	67	0.9	0.366	
	11/5	7.7	120	20	+	0	.....	60	10	6.0	...	...	...	.....	
	12/3	....	180	15	+	0	.....	85	15	5.6	91	38	2.3	.....	
	12/8	....	170	15	+	0	.....	72	25	2.8	103	103	1.0	.....	
	12/15	....	138	30	+	0	.....	115	17	6.7	50	99	0.5	.....	
	12/20	....	210	20	+	0	.....	200	14	14.0	130	149	0.9	.....	
Case 3, D. McC.	10/11	....	225	20	+	0	.....	150−	12	12.0−	44	32	1.3	.....	December 1 to 4 and 8 to 11 inclusive, exposure of tibiæ and femora to Roentgen rays. Dose, 5 milliampere minutes. Discontinued after this time because of low platelet count and prolongation of bleeding time.
	11/1	7.75	240	18	+	0	.....	180	12	15.0	57	52	1.1	0.250	
	12/3	....	180	15	+	0	.....	85	15	5.6	92	38	2.3	.....	
	12/8	....	240	15	+	0	.....	95	25	3.8	...	...	...	.....	
	12/15	7.7	145	30	+	0	160,000	127	17	7.4	116	119	1.0	.....	
	12/20	....	240	20	+	0	.....	180	14	12.0	128	149	0.9	.....	
Case 4, A. S.	6/21	....	150	23	+	0	200,000	73	9	8.0	14	17	0.8	0.378	
	10/29	7.8	210	31	+	0	.....	90	16	6.0	43	37	1.1	0.425	
	11/20	7.7	150	30	+	0	352,000	120	12	10.0	31	28	1.1	0.390	
Case 5, E. O.	10/26	....	305	30	+	0	64,000	170	19	9.0	50	53	1.0	.....	
	11/18	7.6	50	8	+	0	.....	80	17	5.0	120	90	1.3	.....	
	12/15	....	...	..	....	...	248,000	...	..	....	...	...	...	.....	
	12/20	....	120	20	++	0	296,000	200	14	14.0	170	149	1.1	.....	

(NOTE.—Table taken from A Study of the Blood in Hemophilia, by S. H. Hurwitz, M.D., and W. P. Lucas, M.D., Arch. Int. Med., xvii (1916), p. 543.)

* The reaction of the blood was determined colorimetrically by the method proposed by Levy, Rowntree and Marriott, Arch. Int. Med., xvi (1915), p. 389.

lation time but a normal platelet count and normal, though delayed, retractility of the clot.

The condition must have been recognized very early, for it has been recorded that in ancient times there was a dispensation granted by the Jewish rabbis to circumcision in certain families. Bulloch and Fildes* mention the fact that Albucasis, the Moorish surgeon, described the disease as occurring in a certain village where the wounded men died from hemorrhage, and the male children also suffered from bleeding from the gums. The first description of the disease in this country was by Otto† who describes a family history in which the males only were affected, though not all the males showed hemorrhagic tendencies. He pointed out that the females of this family were free from the tendency to hemorrhage but transmitted it to their children. From this time on many reports appeared and in 1820 Nasse‡ proposed a law which goes by his name, namely, that "Males alone are the subjects of hemophilia and that the disease is transmitted by normal females through their marriage with normal males." In 1911 Bulloch and Fildes collected all the known families, amounting to 44. They found that there was a very interesting predominance of male children in these families, amounting to 1246 against 1000 females. The average is usually only a slight predominance of males over females. The mothers who transmit the tendency usually show no signs of the tendency themselves and not all their male children will be affected. According to the Mendelian theory hemophilia is a unit characteristic. It has been traced through at least seven generations and in some of the Swiss villages hemophilia is not an uncommon occurrence and probably extends much further back than the seven generations noted.

Views Concerning the Cause of Hemophilia.—The nature of the explanations offered for the cause of hemophilia varies with the theory of coagulation adopted. If we accept the theory of Howell there are five factors concerned in the clotting of blood, *viz.:* prothrombin, anti-thrombin, thromboplastin, fibrinogen and calcium. All these elements except thromboplastin are present in circulating blood. The main definite feature of the hemophiliac condition is the greatly prolonged coagulation time of the blood after its removal from the vessels, with the precautions necessary to prevent its contamination with tissue juices. All recent workers are agreed that this defect in coagulation is a constant pathological sign of disease but different explanations have been given by different workers to account for the delayed coagulability. Hemophilia has been ascribed indeed to a deficiency in one or another of the various elements which take part

* Bulloch and Fildes, "Francis Galton Eugenics Laboratory Memoirs," London (1911).

† Otto, J. C., "The Medical Repository and Review of American Publications on Medicine, Surgery and the Auxiliary Branches of Science," New York, vi (1803), p. 1.

‡ Nasse, C. F., Archiv. für medizinische Erfahrung im Gebiete der praktischen Medizin und Staatsarzneik under hrsg. von Horn, Nasse and Henke, Berlin (May–June, 1820), p. 385.

in the clotting of normal blood. Wright* in 1893 has attributed the hemolytic condition to a deficiency of calcium. Weil† has given some experimental evidence for the view that delayed coagulability of hemophiliac blood may be caused by the presence of an excess of some coagulation inhibiting body. Sahli‡ and Morawitz and Lossen§, debating the theory of coagulation proposed by Morawitz, have upheld the view that the essential defect in hemophiliac blood may be ascribed to insufficient or defective formation of thrombokinase. This view is shared for the most part by Nolf‖ who believes hemophiliac blood to be deficient in the substance designated by him as thrombozym (thrombokinase, thromboplastic substance). Addis¶ has given experimental proof for the view that the hemophiliac condition is due to a change in the properties of the circulating prothrombin, and Howell** has concluded that not the property but the actual amount of prothrombin is altered in hemophiliac blood. Minot, Denny and Davis†† and Minot and Lee‡‡ have shown that there is a qualitative difference in the platelets (prothrombin element) rather than a quantitative one. They demonstrated that the blood platelets taken from hemophiliac blood required more time to form thrombin than did platelets taken from normal blood and they pointed out that "the delay in coagulation in hemophilia occurs in the initial step in coagulation, which seems to be a rendering of the platelets available by some process like solution . . . in hemophilia with a normal number of abnormally resistant platelets we have a very abnormal coagulation time but a normal bleeding time . . . this defect consists of a slow availability of the platelets for the purposes of coagulation." Hurwitz and Lucas§§ in a study of a series of hemophiliac children demonstrated this same defect in prothrombin, notwithstanding the fact that platelets were often increased in number and never, except in one case reported, had they found the platelets reduced below 100,000; whereas the coagulation time, as is seen in the following case, was markedly interfered with as was also the prothrombin factor though the anti-thrombin and fibrinogen were normal. The clinical history of these cases will be given at the end of this section.

Fonio‖‖ in his work on hemophilia agrees with this conclusion that there is a physiological and quantitative defect in the prothrombin factor.

* Wright, A. E., Brit. Med. Jour., London, ii (1893), p. 223.

† Weil, P. E., Presse Med., Paris, xiii (1905), p. 673.

‡ Sahli, H., Ztschr. f. klin. Med., Berl., lvi (1904–5), p. 264; Deutsches Arch. f. klin. Med., Leipzig, xcix (1910), p. 518.

§ Morawitz, P., and Lossen, J., Deutsch. Arch. f. klin. med., xciv (1908), p. 110.

‖ Nolf, P., Ergeben. d. inn. Med., x (1913), p. 275.

¶ Addis, T., Jour. Path. and Bact., xv (1911), p. 427.

** Howell, W. H., Arch. Int. Med., xvii (1914), p. 76.

†† Arch. Int. Med., xvii (1916), p. 101.

‡‡ Arch. Int. Med., xviii (1916), p. 474.

§§ Arch. Int. Med., xvii (April, 1916), pp. 543–569.

‖‖ Fonio, Cor. Bl. f. Schweiz. Aerzte, xlv (1915), p. 1505.

Symptoms.—The symptoms of hemophilia usually appear during the first year though they may not appear until later in childhood. Most of the hemorrhages can be directly connected with some trauma though this is usually much less than that which would produce hemorrhage in a normal child, or they may be first evidenced by a simple operation such as circumcision. Epistaxis may be one of the first evidences of this condition. Hemorrhages from the mucous membranes from slight abrasions into the subcutaneous tissues or into the muscles and joints are common. After slight trauma oozing will persist for hours or days. A clot will form, but it takes so long for it to retract that it will be lifted up by the continuous oozing and is soon floated away, but re-clots again and goes through this process hour after hour. This at times continues until there is a marked anemia produced and when one thinks that the end must come from the loss of blood at times the oozing will stop suddenly and the patient make a rapid recovery. But even at this time if the blood is examined there will be found an increased number of platelets and the same defect, though sometimes not quite so marked in the prothrombin factor. We have followed several cases for years, examining them for prothrombin time at various intervals and have never found them absolutely normal. The prothrombin time apparently goes in waves and has nothing directly to do with the appearance of hemorrhage, the tendency for which is always present but the initiation of which usually develops following some trauma. It is a common experience that deep punctures or venepunctures do not produce hemorrhage. One of the most characteristic lesions are the hemorrhages into the joints, the knee and elbow joints being most frequently affected. The hemorrhage at first is often absorbed but sooner or later there is definite destruction of the epiphyses with marked hypertrophy. *X*-rays on the joint in cases we have studied have shown very definite hypertrophic changes associated with what appears to be calcium deposits. The epiphyses often show cavities. Such joints should not be mistaken for either arthritis or tubercular arthritis. They are usually not associated with temperature, come on suddenly, and a definite history of repeated hemorrhages in our experience can always be obtained. There is very little elevation of temperature and until there has been marked disability or limitation in motion there is no atrophy of the muscles. There is constant tendency for repeated occurrence, though usually only one joint is affected at a time; however, we have seen as many as four joints involved in quick succession and all essential signs at the same time. The outcome of these hemorrhagic cases is very doubtful. Few live to adult life though some have been reported as living to old age. They either succumb to the hemorrhage or die of intercurrent infection as one of the cases which we have been following for some time lately died of acute pneumonia. Previous hemorrhages occurred and at autopsy hemorrhages into some of the serous cavities were found without any definite change beyond the hemorrhages in any of the organs or in the bone marrow,

though the extensive hemorrhages made it rather difficult to say definitely whether minute changes had occurred or not. Fifty per cent. of the cases die before the seventh year and according to Ettlinger* the greatest number of deaths occur during the first year. Undoubtedly many cases have died during infancy who have been considered ordinary hemorrhagic disease of the newborn rather than hemophilia.

Pathology and Physiology.—We have studied the blood protein and found the total protein, though somewhat diminished, is practically normal. The globulin fraction shows a slight relative excess but these differences are too small to possess any real significance. There is apparently no abnormality in protein products arising during the clotting of hemophiliac blood. The non-protein constituents were normal also.

Experimental Work.—The only experimental work which has been done with animals is that reported by Maclean† and by Howell and Holt.‡ These workers have demonstrated the anti-coagulating action of two phosphatides, and that the injection of these phosphatides into dogs resulted in blood findings which were similar to those of hemophilia. The dogs bled from wounds and the blood was found to act much like hemophiliac blood.

Diagnosis.—Diagnosis is or should be comparatively easy except perhaps in primary hemorrhage. With our modern methods of blood study it should not be difficult to determine prolonged coagulation time and the defect in the prothrombin factor. The only condition from which it may be difficult at times to make a differential diagnosis would be chronic purpura hemorrhagica and hereditary telangiectases —Osler.§ Purpura hemorrhagica occurs both in males and in females. There is usually no family history of bleeding in other members of the family. All hemorrhagic lesions in purpura hemorrhagica appear as superficial purpuric areas and not as subcutaneous hemorrhagic areas. Hess‖ has pointed out what he calls the tourniquet test to differentiate purpura hemorrhagica from hemophilia. In purpura hemorrhagica petechiæ appear, whereas in hemophilia they do not when a tourniquet is applied. In purpura hemorrhagica the joints are very rarely affected whereas in hemophilia they practically always are. The blood in the two conditions is entirely different. In purpura hemorrhagica the bleeding time is prolonged whereas in hemophilia it is normal. The coagulation time is normal in purpura hemorrhagica and prolonged in hemophilia. The platelets are normal in number in hemophilia and markedly reduced in purpura hemorrhagica.

* Ettlinger, V. v., Jahrb. f. Kinderh., Leipzig, iv, 3 F. (1901), p. 24.

† Maclean, J., Amer. Jour. Physiol., Boston, xli (1916), p. 250.

‡ Howell, W. H., and Holt, Amer. Jour. Physiol., Boston, xlvii (1918–19), p. 328.

§ Osler, Sir Wm., Bull. J. H. H., xii (1901), p. 333, and xviii (1907), p. 401, and Quarterly Journal, i (1907–8), p. 53.

‖ Hess, A. F., Arch. Int. Med., xvii (1916), p. 203.

The clot is normal in hemophilia and firm when it does form, whereas in purpura hemorrhagica it is soft and non-retractile. The prothrombin time is normal in purpura hemorrhagica and markedly delayed in hemophilia. We differentiate this condition from congenital telangiectasis because bleeding is usually from the nose. It affects both males and females. There is a strong family history record in many members of the family but other areas of telangiectases are found over the body. The blood in telangiectases is normal; there are no defects in coagulation time. The bleeding is purely a mechanical tearing of the vessels over these areas.

Treatment.—There is no specific treatment. Many remedies have been advocated for stopping the bleeding. In our opinion none of the specifics are of any value. Calcium is valueless as is gelatin. The local application of fresh blood or fresh tissue, or what is better, cephalin prepared according to Howell's method and described by Maclean,* has been used by us with good results locally, though not always with the same efficacy even in the same individual at various times. This, however, may depend upon the factor of deterioration in the cephalin. As pointed out by Maclean, cephalin deteriorates if allowed contact with the air. Cephalin is an unsaturated phosphatide which loses its thromboplastic power because of oxidation or reduction if exposed to the air. Under Maclean's direction Hynson, Westcott and Dunning of Baltimore have prepared a gauze saturated in cephalin and put up sterilely in vacuum sealed tubes, for local application. Freshly prepared cephalin can be used. This can be prepared from brains obtained from the slaughter house, ground up and dried, powdered and extracted with ether for three or four hours. The ether is then filtered off and repeated until the filtration is practically clear. The filtrate is then dried before an electric fan, the residue is extracted with acetone and then extracted twice with alcohol. This is then dried and kept in a dark place in a vacuum. We have been able to use this both by administration by mouth in solution, or, after sterilizing, intermuscularly. Maclean and Howell† report very definite results from administering this orally. Our results were not as good as reported by Maclean probably because we did not continue the oral administration over as long a period. It is to be highly recommended that hemophiliacs should be kept on such treatment over long periods with intermittent studies of their blood. This is the only way in which definite conclusions of the value of cephalin as a prophylactic as well as a curative measure can be obtained. During acute hemorrhage, however, cephalin in our experience is not sufficient to stop hemorrhage. Though we have never administered it intravenously there is no reason why this should not be done because it will stand sterilization and in 1 per cent. solution at least we have found it to produce no ill effects in animals. Intermuscularly it is rather painful. During the acute hemorrhages, however, there is no treatment comparable to

* Maclean, J., Am. Jour. Physiol., Boston, xliii (1917), p. 586.

† Howell, W. H., "Harvey Lectures," Phila. and London, series 12 (1917), p. 273.

that of indirect blood transfusion. One must be prepared to repeat blood transfusion very often because, as has been pointed out, the life of the platelet is only approximately three days so that the value of transfusion cannot be expected to last longer than this period. Indirect transfusion restores temporarily the platelets and so gives the organism an opportunity, in some unknown way, to regain a certain equilibrium. At least we have found that notwithstanding the fact that the prothrombin element returns to its abnormal state within a very few days, as has also been pointed out by Minot and Lee, very often after a single transfusion or after two or three transfusions the bleeding will stop and the patient rapidly regain his normal well-being. The anemia is also by this measure more rapidly corrected and the life of the red cells being longer this lasts much longer. Where operations are contemplated transfusion should always be given to hemophiliacs just before operating and if the wound is not healed within 48 hours transfusion should be repeated. It may be necessary to repeat the transfusions several times. One should not wait for hemorrhage to reappear before transfusing. It is much safer to transfuse before hemorrhage occurs because, if there is any wound, hemorrhage will unquestionably recur from 48 to 96 hours after transfusion. By this procedure, tonsillectomy, extraction of teeth and major operations can be performed with a fair hope of the hemophiliac escaping a period of hemorrhage. It is not to be expected that this will do anything but tide over a critical period. The condition is not curable though most patients as they grow older seem to acquire an ability to protect themselves against the type of trauma that causes hemorrhage. These patients should lead a very careful and regulated life on a full diet and should not enter into athletics. During the acute periods of hemorrhage, besides the efforts directed towards checking the bleeding, complete rest in bed, and, where the joints are involved, putting them up in splints and protecting them as far as possible, will diminish the tendency towards permanent damage, by increasing absorption. As suggested by Maclean, these patients should carry with them cephalin gauze to apply immediately if they do have a trauma, for the sooner the hemorrhages are checked, obviously the better it will be for the patient.

Atypical Cases That Somewhat Resemble Hemophilia.—Addis* says that purpuras may be divided into three groups: (1) Patients who always show signs of hemorrhage or are seldom free from hemorrhage. These cases are typical cases of purpura hemorrhagica which usually die early. (2) Those in whom hemorrhage occurs due to slight trauma, and (3) a group occurs in which hemorrhage only follows severe trauma. These cases usually give a history of bleeding over a long time after severe wounds, or it may occur for the first time when operated upon. There is another group which perhaps is somewhat closely allied to the hemophilias which simply show on bruising black and blue marks, or they may have, on being wounded,

* Addis, T., Jour. Path. and Bacteriol., xv (1910–11), p. 427.

hemorrhage for a short time. Such cases often do not show any disturbance in their blood between the periods of hemorrhage. At the time they are experiencing a hemorrhage, however, their blood will often show prolonged coagulation, though not nearly so long as the typical hemophilia and the prothrombin time is increased. They will also exhibit the re-clotting phenomena; otherwise their blood is normal. Other cases will show simply black and blue areas from very slight bruises, but will not have a tendency to bleed. They will give a history of having a tendency to epistaxis but not other hemorrhages. These black and blue areas are usually only found on examination for some other condition. We have seen several in which the mothers have said that the child always has one or more black and blue areas and often the mothers will give a history of having the same condition. In one of the cases which Hurwitz and Lucas* report the mother stated that she had noted black and blue spots appear occasionally on different parts of her body following slight trauma, she had had frequent attacks of epistaxis and had had one profuse hemorrhage following extraction of a tooth.

The blood in such mild cases usually, as far as our experience goes, shows no abnormalities. Such border line cases undoubtedly will be observed more in future than they have been in the past and perhaps, in certain periods, these cases may show slight abnormalities in their coagulation factors. They, however, should not be confused with true hemophilia and for this reason we have separated them from that condition.

Hemorrhagic Periods Associated with Other Conditions.—It has been pointed out that the other factors of the blood besides prothrombin or platelet deficiency may cause hemorrhage. Such abnormalities of other factors occur often definitely associated with temporary lesions in certain organs. In diseases of the liver, especially destructive jaundice, there is a definite change in the blood which, as has been shown by Lee and Vincent,† is definitely associated with a lack of available calcium-ions. In such cases there may be prolonged bleeding though often bleeding will not occur unless there is some operation. The lack of available calcium can be shown by the addition of calcium to the blood *in vitro*. Whipple and Hurwitz‡ have pointed out that with chloroform poisoning the fibrinogen of the blood is altered and hemorrhage due to this may occur in the newborn where the mother has received chloroform. On the other hand, some of these hemorrhages of the newborn are undoubtedly due to an excess of anti-thrombin, as has well been pointed out by Whipple, which is also due to defective functioning of the liver. Lately Haessler and Stebbins§ have shown that the presence of as little as 5 per cent. of bile will inhibit the fibrinogen and prothrombin from acting. The action

* Arch. Int. Med., xvii (1916), p. 543.
† Lee and Vincent, Arch. Int. Med., Vol. XVI (1915), p. 59.
‡ Jour. Exper. Med., xiii (1911), p. 136.
§ Haessler and Stebbins, Jour. Exper. Med., xxix (1919), p. 445.

of bile, as has already been pointed out has been shown by Sellards to be a photodynamic property which acts only in the sunlight and not in the dark. We have several times spoken of hemorrhages which occur in association with sepsis. This is one type of hemorrhage of the newborn, in which case it is usually fatal. In many septicemias where chronic or acute hemorrhage may occur it may be associated with purpuric areas, as has been stated, which are produced by bacterial emboli. In these cases anti-thrombin is probably the factor which is increased and the coagulation time will be increased though the platelets will often be found to be increased rather than decreased. Not in all cases in which the coagulation time is increased will hemorrhage appear, for it has been demonstrated that in such conditions as lobar pneumonia where coagulation time is increased bleeding rarely occurs. In association with nephritis, both acute and chronic, hemorrhage may occur. This is seen in the chronic nephritis following scarlet fever. It may sometimes be associated with purpuric areas, and also with epistaxis. None of these conditions can be called true hemorrhagic conditions but they can only be differentiated by careful study of the blood at the time.

CHAPTER LXXIX

HODGKIN'S DISEASE OR LYMPHADENOMA

By William Palmer Lucas, M.D., and E. C. Fleischner, M.D.

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This condition is characterized by enlargement of the lymphatic glands and of the lymphoid tissue throughout the body associated with progressive anemia. Towards the end, which is always fatal, the picture may become one that resembles sepsis with terminal fever.

Etiology.—The disease is very infrequent in infants and more frequent between the fifth and tenth years and again between the fifteenth and twentieth, though before 20 years of age it is a comparatively rare disease. It is much more frequently found in males than in females, in the ratio of about three to one. The disease is not hereditary nor contagious. There has been no definite etiology established for the condition. It seems to be more often associated with focal infection, especially infections of the pharynx, tonsils and teeth; in other words, associated with chronic infections of the upper respiratory tract. With a certain amount of constancy a diphtheroid organism has been isolated by many workers, particularly in this country by Buntting and Yates* and by Rosenow.† These organs have been isolated both from the glands and by Rosenow from the blood stream during the acute stage of the disease. Buntting and Yates have also reported that they have been able to produce a similar condition in monkeys and laboratory animals. Billings, however, cautions against accepting this organism as a causative factor because diphtheroid organisms are found so frequently in tissue which is diseased or tissue of low vitality.

Pathology.—There are few conditions in which the lymphatic glands show such a marked enlargement. It comes on slowly but is progressive. The glands tend to remain discrete but are tightly bound together giving the appearance of great lobulated masses which can be easily felt or seen. When the glands first enlarge they may be soft but fluctuation is not felt. As the glands increase in size fibrinous tissue increases greatly which becomes very hard and firm. In agreement with this, if the glands are opened early the glandular structure will be made out. As the glands hypertrophy, however, the general glandular structure disappears and gradually nothing but connective tissue will be apparent, though on close examination small

* Buntting and Yates, Arch. Int. Med., xii (1913), p. 236.

† Rosenow, Jour. Amer. Med. Assn., lxi (1913), p. 2122.

islands of glandular tissue can usually be made out. The early glands show an increase in the lymphocytes, the picture being an active lymphocytic hyperplasia. Later on this is replaced by an increase in the reticular cells, endothelial cells and fibroblasts. As the process develops the fibroblasts increase and the endothelial cells take on the characteristic of giant cells which usually have a single large round nucleus. The nucleus, however, may be lobulated and somewhat resembles in appearance the megacaryocytes of the bone marrow. At times glands will be found with marked infiltration with other cells particularly eosinophils. These may sometimes be very abundant. At times the predominating cells are myelocytes, but they are probably produced locally and do not immigrate from the bone marrow. In rapidly progressing cases a necrosis may occur, especially of the endothelial cells. At times this is mistaken for tubercular involvement but the typical giant cells are absent and the presence of eosinophils is more characteristic of Hodgkin's disease. At times the predominating cells may be endothelial, giving the appearance of an endothelioma, though usually the predominating cells are lymphocytes. All organisms which contain lymphoid tissue are involved. The spleen may become enlarged and is usually so in the acute cases. The liver may also be enlarged and there is found the same lymphoid tissue. The pathological picture therefore in some cases resembles leukemia, and in others it would appear as if it were due to an infective cause.

Symptoms.—The cervical glands are usually affected first. Next in order are the axillary, inguinal, retroperitoneal, mediastinal, bronchial and mesenteric glands. The onset is so gradual at times that this period may be spoken of as a latent period. Then comes a definite period of progress when the disease becomes widespread and lastly the septic symptoms appear which usually ushers in the final stage. Throughout the course there are different periods when the process progresses very rapidly, other periods when there seems to be either a very slow progression or a standstill. The patient usually complains meanwhile of fatigue and lassitude. In the majority of cases, as has been stated, the first involvement is that of the cervical glands. This occurs in from 50 to 80 per cent. of cases. Usually one side is involved before the other and a group of glands will be involved rather than a single gland. As the process develops and several groups of glands are involved anemia begins to appear. It is of the secondary type and usually not extreme until the final period or stage is reached. When the bronchial or mediastinal glands are involved pressure symptoms indicated by shortness of breath or cough appear. Various symptoms will occur dependent upon what particular chain of glands is involved. In the final stage, or in acute Hodgkin's disease, progress is very rapid. Patients often resemble an acute infection, with high temperature, gastro-intestinal symptoms, vomiting, and diarrhea, and the glands during this period may become quite painful and tender, as may also the spleen. Once the patient has passed into this stage they rarely have an intermission but go on to a fatal termination.

The same is true of the type of acute Hodgkin's disease. In these cases they rarely have any intermissions. The course is a continual stormy progression which usually ends fatally within three or four months. Skin involvements in the chronic cases are not so common in children as in adults though they may occur as lymphatic nodules.

The blood in Hodgkin's disease shows a slight increase in the lymphocytes early, which gradually declines while the eosinophils increase. At the same time there is usually an increase in the basophilic cells or large mononuclears. The total cell count rarely goes over 15,000 or 20,000 and as the disease progresses the polymorphonuclears increase. As the condition progresses a further change in the blood picture occurs. The eosinophils and basophils which at one time were increased now diminish and may almost disappear. In acute cases this may occur early so that the first lymphocytosis and eosinophilic and basophilic stages of the blood picture may be entirely lacking. The blood platelets are usually increased and tend to be larger than normal.

Diagnosis.—There is no condition in which there is such a marked general enlargement of all the lymph glands as in Hodgkin's disease. Rarely even in tuberculosis do we see such a general enlargement, and when there is a general enlargement in tuberculosis the glands tend to break down and to fuse whereas in Hodgkin's disease as the condition progresses the glands tend to become harder and firmer. The von Pirquet reaction is also of assistance in differentiating the two conditions and the blood picture in tuberculosis gives a definite lymphocytosis, whereas, as we have seen, the lymphocyte stimulation in Hodgkin's disease is only very early and they rapidly diminish in number. This is often of importance in differentiating the two conditions. In tuberculosis the eosinophils are rarely increased and the large mononuclears do not tend to be increased, whereas in Hodgkin's disease, especially in the earlier stages, both the eosinophils and large mononuclears are increased as the lymphocytes decrease. In acute tuberculosis, as has been pointed out by Murphy, the lymphocytes may be reduced, in which state the blood picture may resemble somewhat that of Hodgkin's disease though in this type of tuberculosis the glands never approach the size that they do in Hodgkin's disease.

Prognosis.—Hodgkin's disease is always fatal. The duration of the disease may be from a few weeks to several years but no case has ever been reported as having recovered.

Treatment.—Treatment can only be palliative. In the acute cases there is nothing that can be done; in the more chronic cases radical surgical excisement if the glands are superficial is the only procedure. All focal areas of infection should be removed, especially tonsils, adenoids and teeth. In operating, the surrounding tissue should be carefully cleaned away as this tissue may be in itself a source of secondary involvement. Of late, the application of cross-fire radiation with *x*-rays or radium has been advised. This is probably the only means of treating the deeper glands. Treatment with vaccine

prepared from the diphtheroid organism or with immune sera, as suggested by Billings and Rosenow and by Buntting and Yates, may be tried but they do not offer much hope for permanent cure. They are undoubtedly of secondary value as compared with radical surgical treatment when that is possible.

Along with surgical treatment, general hygienic and dietary treatment and careful régime should always be planned. Arsenic in the past has always been given though it is of doubtful value.

CHAPTER LXXIX

BLOOD TRANSFUSION IN INFANTS AND CHILDREN

By Lester J. Unger, M.D.

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The idea of transferring blood was conceived by Denis in 1667. Blundell was the first to report a series of blood transfusions. Modern methods, however, began with the introduction by Carrel of the technique of suturing vessels one to another. Numerous ingenious devices such as the Crile and Elsberg cannulas have been suggested to overcome difficulties attending the anastomosis of vessels. None have survived the practical test, so that indirect methods have gradually taken their place. These are of two types: Those supplying whole, unmodified blood, and those which add an anti-coagulant. The first group is represented by the methods of Kimpton and Brown,* of Lindemann† and of Unger.‡ The second group is represented by the citrate method.

Kimpton and Brown utilize a special graduated cylinder the inner wall of which is coated with a thin layer of sterile paraffin. The desired amount of blood is allowed to run into this cylinder after its beak has been inserted into the donor's vein. The beak is then inserted into the vein of the patient and the cylinder emptied of blood.

By the Lindemann method blood is transferred by means of a series of 20 c.c. Record syringes. A needle is inserted into the vein of the recipient and another into that of the donor. Blood is aspirated and the filled syringe is given to an assistant to inject. Occasionally saline solution is also injected to avoid clotting. At least six syringes are necessary. Each syringe after emptying must be washed in saline solution until free from blood.

The Unger method utilizes a special instrument consisting of two channels by means of which a Record syringe is connected alternately with a vein of the donor and a vein of the recipient. At the time the syringe is connected with the donor for the aspiration of blood, a syringe with saline solution is connected with the recipient and vice versa. This immediate and continual flushing of the channel through which blood is not passing insures freedom from clotting. The instrument is connected to the cannulas after they have been inserted

* Kimpton and Brown, Boston Med. and Surg. Jour, clxix (1913), p. 783.

† Lindemann, Med. Rec. (1912), p. 979; Am. Jour. Dis. Chil. (1913), p. 28.

‡ Unger, L. J., A New Method of Syringe Transfusion, J. A. M. A. (Feb. 13, 1915), p. 582; Recent Simplifications of the Syringe Method of Transfusion, *Ibid*, (Sept. 18, 1915), p. 1029.

through the skin into the veins of the recipient and donor. A Record syringe is then inserted into the instrument and blood is aspirated. When the syringe is filled the stop-cock is turned and blood is injected.

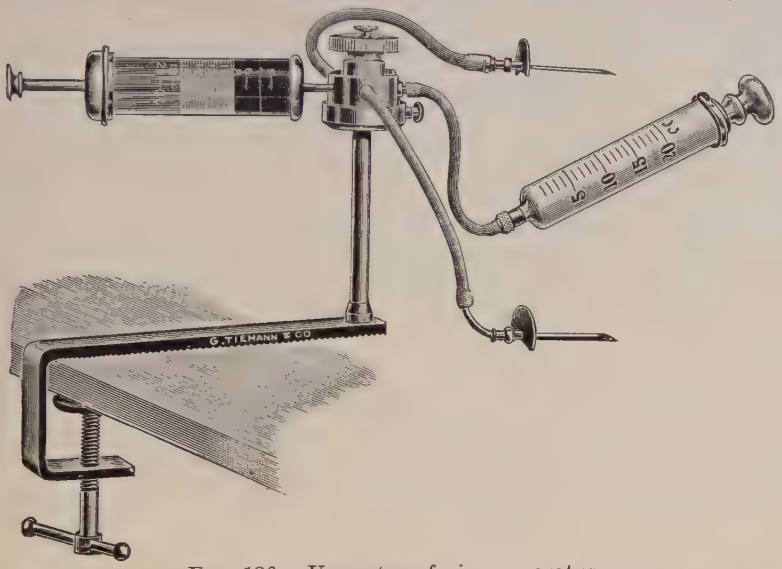

FIG. 136.—Unger transfusion apparatus.

FIG. 137.—Blood transfusion.

Simultaneously normal saline solution is forced through the channel which is not being used for the aspiration or injection of blood. This procedure is continued until the desired amount of blood has been

transfused. In order to prevent clotting in the syringe a stream of ether is played on its barrel while it is being filled with or emptied of blood. In this way only one syringe is required, regardless of the amount transfused.

The methods which utilize an anti-coagulant are best represented by the so-called citrate method. According to this technique a needle is inserted into a vein of the donor and blood is allowed to flow into a receptacle containing a 2 per cent. solution of sodium citrate. Ten cubic centimeters of this solution is used for every 90 c.c. of blood. As the blood flows into the receptacle it should be continuously stirred. When the desired amount has been collected this citrated blood is given to the patient, using the technique for intravenous infusions.

The relative merits of unmodified blood and of blood modified by means of sodium citrate* is of active interest in connection with the subject of blood transfusion. From a biologic point of view the delicate blood tissue is changed by the chemical and physical alterations brought about by adding sodium citrate and by its sojourn outside of the vessels. Unmodified blood, however, flows almost from vessel to vessel and is given to the patient in an unchanged condition. For diseases, therefore, in which the transfer of blood is indicated for itself, that is, where it is required as a tissue—as in the various anemias, blood diseases and infections—there can be no question as to the superiority of whole unmodified blood. In cases of hemorrhage, on the other hand, when the purpose is not so much to replace pathologic with normal blood but rather to replenish the impoverished circulation or to bring about cessation of hemorrhage, citrated blood may serve as a substitute.

This position is based not only on clinical experience but also on laboratory findings. Clinically, Drinker and Brittingham† have noted that after citrate transfusions a chill occurs in about 57 per cent. and febrile reactions in 60 per cent. of cases. By the Unger method, which supplies unmodified blood, a chill occurs in about 3 per cent. of cases and febrile reactions in about 10 per cent. Drinker and Brittingham have shown that these reactions are due to changes in the blood platelets which have undergone alterations coincident with early coagulation. They also demonstrated that the mere addition of sodium citrate to blood causes slight abnormality of the red bood-cells as evidenced by an increased fragility and increased tendency to hemolyze.

It has been maintained by some that because of its simplicity the citrate method renders all other procedures unnecessary. Recently,‡ however, medical opinion seems to be shifting in the opposite direction.

* The Therapeutic Aspect of Blood Transfusion, J. A. M. A., lxxiii (1919), p. 815. Unger, L. J., The Deleterious Effect of Sodium Citrate Employed in Blood Transfusion, *Ibid.*, lxxvii (1921), p. 2107.

† Drinker, C. K., and Brittingham, H. H., Transfusion Reactions, Arch. Int. Med., xxiii (1919), p. 133.

‡ Bernheim, B. M., Whole Blood Transfusion and Citrate Blood Transfusion, J. A. M. A., lxxvii (1921), p. 275.

Harmful results following the chill, fever and shock coincident to citrate transfusions have been noted. In fact death has been reported as one of the sequelæ.

Laboratory tests demonstrate differences between unmodified and citrated blood. It has been shown* that although Wassermann tests on serum are negative, similar tests on plasma of the same individual, after it has been citrated as for transfusion, are slightly anti-complementary. An anti-complementary reaction signifies that a substance is present which of itself is able to inactivate complement. This proves, therefore, that plasma of blood given in citrate transfusions contains a substance which inactivates complement and which is not found in serum of unmodified blood taken from the same donor. By a series of experiments it has been proved that this substance is extracted from red blood-cells by the action of sodium citrate directly on the cell wall.

It has also been shown that complement is further diminished by the direct destructive action of sodium citrate. When a citrate transfusion is performed, blood is being given in which complement has been diminished in two ways—first by the production of an anti-complementary substance which inactivates available complement and second by a direct destructive action on complement. This is of practical importance, since one of the indications for blood transfusion is infection, local and general, and complement is a vital factor in the defense against pathogenic organisms. It plays an important rôle in destroying bacteria.

Another method of defense against pathogenic organisms is the phagocytic power of white blood-cells. This power of the white cells in unmodified blood is far greater than that in citrated blood. This can be demonstrated in the following way: In one series test the normal washed cells, in another test the cells from the same individual after they have been affected by sodium citrate. In both sets use *Staphylococcus pyogenes aureus* and the serum obtained from the person who has supplied the cells. It has thus been found that as much as 75 per cent. of the phagocytic power of white cells is destroyed by sodium citrate.

The opsonins in serum are also greatly interfered with by the addition of sodium citrate. This marked reduction in the power of blood plasma to prepare bacteria for ingestion and the great destruction of the inherent power of white cells to ingest bacteria renders citrated blood of less value than unmodified blood when transfusion is employed to combat infection.

The observation was made first by Landsteiner† in 1900 that, when the serum of certain individuals was mixed with cells of other individuals, clumping of the corpuscles, or iso-agglutination, occurred.

* Unger, L. J., The Deleterious Effect of Sodium Citrate Employed in Blood Transfusion, J. A. M. A., lxxvii (Dec. 31, 1921), p. 2107.

† Landsteiner, K., Centralbl. f. Bakteriol., xxvii, Part I (1900), p. 357; Wien. klin. Wchnschr., xiv (1901), p. 1132.

Moss* and also Jansky† showed that people could be divided into four groups (Table 1) according to the way their blood interagglutinated. These groups are established by agglutinins in serums and receptors for these agglutinins in cells.

TABLE 1

AGGLUTINATION OF SERUMS OF THE FOUR GROUPS*

Corpuscles	Serums			
	Group I	Group II	Group III	Group IV
Group I	0	+	+	+
Group II	0	0	+	+
Group III	0	+	0	+
Group IV	0	0	0	0

*The plus sign indicates agglutination. The corpuscles of Group I are agglutinated by the serum of all other groups, but its serum has no agglutinating properties. The serums of Groups II and III mutually agglutinate each others' corpuscles. Group IV serum agglutinates all other corpuscles, while its own corpuscles are not agglutinated by any serum.

The classification of individuals according to their iso-agglutinin reactions is of practical importance in relation to transfusion. It has rendered transfusion safe. This safety, coupled with simplification of technique, has established transfusion as an extremely important therapeutic measure. By examining under the microscope a mixture of the patient's cells (diluted with saline solution) and Group II serum and also a similar mixture of cells with Group III serum, the group of the patient can be established (Table 1). It has become customary to determine the "group" of the patient and then transfuse blood of a donor of the same "group," provided he has no blood disease and his hemoglobin and red cell count is normal. Although, in the majority of cases, the bloods of donor and patient belonging to the same group are compatible, the number of exceptions is sufficiently great to warrant a different procedure and greater caution. Occasionally, although the donor and patient are of the same group, when the bloods are tested one against the other a small number of agglutinated clumps of red blood-cells will be seen. Such donors should be rejected. If they are used a sharp reaction—chill and fever, undoubtedly due to the occurrence of agglutination—may occur.

The recognized "group" of an individual is established by the presence of a "chief" or "major" agglutinin in his serum. Agglutination of cells by serums of the same group is probably due to a "para" or "minor" agglutinin which causes a lesser degree of agglutination. The transfusion of such blood gives rise to clinical reactions. This

*Moss, W. L., Bull. Johns Hopkins Hosp., xxi (1910), p. 63; xxii (1911), p. 238.

†Jansky, J., Sborn. Klin., viii (1906–1907), p. 85.

disagreeable result, however, can be eliminated by testing the blood of every prospective donor directly against the patient's blood and by careful microscopic examination of the mixtures. This phenomenon of major and minor agglutination of red blood-cells is comparable to that of group agglutination of bacteria. As is well known, a serum containing a high agglutinative power against typhoid bacteria may to a lesser degree also agglutinate bacteria belonging to the same group, such as paratyphoid or colon bacilli.

Another important but atypical result is encountered when performing the usual agglutination and hemolysis tests in infants. It has been shown often that the agglutinins for bacteria in normal non-immunized animals are not present in newborn animals but are acquired later in life. So also with the agglutinins for red blood-cells.

Halban* was first to note this difference between blood of a mother and that of her infant. He found that the agglutinating power of a mother's serum was far greater than that of blood taken from the umbilical cord of her infant. Agglutinins are present in the serums of about 13 per cent.† of infants under one month of age, whereas the average among adults is 97 per cent. The percentage of children whose serums contained agglutinins increases with their ages, but reaches the adult average only between the second and fourth years of life (Table 2).

TABLE 2

INFLUENCE OF AGE ON APPEARANCE OF AGGLUTININS IN SERUM AND RECEPTORS IN CELLS*

Age	Number of children tested	Serum contained agglutinins		Corpuscles agglutinable	
		Number	Per cent.	Number	Per cent.
From birth to 1 month	24	3	13	6	25
From 1 month. to 6 month	16	4	25	8	50
From 6 month. to 1 year	18	9	50	9	50
From 1 year. to 1½ years	18	12	67	10	55
From 1½ years. to 2 years	11	7	66	7	66
From 2 years. to 4 years	32	30	94	21	66
Total	119				

* The normal adult percentage for agglutinins in serum is reached between the second and the fourth year of life, while that for receptors is reached at six months.

The same thing is true of cells. The great majority of children are born with cells possessing no receptors—they cannot be agglutinated by any serum. The cells of only about 35 per cent. of newborn infants can be agglutinated, whereas in adults the average is 50 per cent. The

* Halban, J., Wien. klin. Wchnschr., xiii (1900), p. 545; Halban, J., and Landsteiner, K., München. Med. Wchnschr., xlix (1902), p. 473.

† Unger, L. J., Precautions Necessary in the Selection of a Donor for Blood Transfusion, Jour. Amer. Med. Assoc., lxxvi (1921), p. 9.

acquisition of receptors occurs at about six months, far earlier than the appearance of agglutinins in the serum. In a few cases, receptors antedate agglutinins.

Naturally, if the full quota either of agglutinins or of receptors is wanting, the blood fails to conform perfectly to established adult groups. At about four years of age, almost all children have established their adult iso-agglutinin group. The acquisition of a full quota either of agglutinins or of receptors may occur gradually. Serum may contain agglutinins for cells of Groups I and III, and later acquire them for Group II cells. Thus the child apparently has changed its group.

From the practical point of view, these facts render it comparatively simple to find a donor compatible for transfusing an infant. The blood-cells of most children under six months cannot be agglutinated, and their serum cannot agglutinate a donor's cells. For such children, any donor, regardless of group, is compatible. I have performed transfusions many times in such cases without any untoward results. *It is therefore superfluous to attempt a grouping of an infant's blood. One should rather test the blood directly against that of the prospective donor.*

The peculiarities of infant's blood probably explain the frequent statement that any mother may be used as a donor for her newborn infant. This is, however, absolutely erroneous. The incompatibility is occasionally such that if the mother is used as donor for her infant the result might be disastrous. It is therefore necessary to test the blood preliminary to transfusion. Children of the same family often belong to different groups. Among six sisters of one family tested all four groups were represented, and two of these women differed in grouping from their children.

It is believed commonly that the cells of Group IV cannot be agglutinated by any serum. A person of this group is accepted as a "universal" donor. By this term is meant a donor who in an emergency may furnish blood to any patient regardless of group, on the theory that danger arises only when the donor's cells are agglutinated, and that agglutination of the patient's cells may be disregarded. Very occasionally, however, serum may agglutinate cells of certain Group IV donors. A result of this kind demonstrates the inadequacy of "typing" merely the patient, and *the necessity of testing the blood of donor and patient, one against the other.* Some patients will show the phenomenon of auto-agglutination—that is, the cells of the patient are agglutinated by his own serum. Blood containing auto-agglutinins will clump its own cells when its temperature is lowered, the clumping disappearing when the temperature is raised to 37°C. Unless one is aware of this phenomenon a patient's blood may be classified erroneously in Group I. Special care must be taken to determine the proper grouping of such bloods. The cells should be washed repeatedly in warm saline solution until a suspension shows no auto-agglutination when placed in the ice-box.

Certain serums will produce a rouleaux formation of the patient's cells. This reaction is quite different from agglutination, and often can be eliminated by using a weaker emulsion of cells or by diluting the serum. The rouleaux-forming substance in serum can act on cells of any group. I have transfused several patients with apparently no ill effect—no untoward reaction—whose serums contained this substance.

The safest route for the introduction of blood in infants is by way of one of the veins on the anterior aspect of the elbow. Frequently a needle can be inserted directly through the skin into one of these veins without any preliminary incision. This has been done in children a few hours old. If it is impossible, however, a transverse incision one-fourth of an inch long should be made directly over the most prominent vessel. If the incision is made in one of the creases found here, it is almost impossible, after a lapse of about six months or a year, to detect the site of incision.

The superior longitudinal sinus has been urged as a convenient route for the transfusion of blood. If the inferior wall of this sinus is accidentally perforated by the needle there is danger of injecting blood on the brain or of active hemorrhage occurring, especially since these patients usually have a hemorrhagic tendency. Employing this route for aspirating blood for examination in non-hemorrhagic cases (Wassermann, blood cultures, etc.) is quite another matter.

The amount of blood transfused varies with the age of the child and the condition of his heart and lungs. In newborn infants the dose varies from 60 to 150 c.c. In older children as much as 500 c.c. may be given. In cases of hemorrhage one is guided by the amount that has been lost. In pneumonia the amount should be comparatively small and repeated if necessary. It has been recommended* that for children under two years of age, 16 c.c. per pound of body-weight should be transfused. In older children, however, the amount in proportion to the weight is less than this. The color of the child's face is an excellent guide. When a healthy pink color appears the proper dose has been given. The transfusion should never be continued to the point at which cyanosis appears.

The **indications**† for blood transfusion are: (1) Hemorrhage; (2) diseases of the blood; (3) toxemias; (4) nutritional disturbances; (5) shock; (6) infection.

1. Hemorrhage.—This is one of the conditions in which blood transfusion is the ideal treatment. It serves not only to replace blood which has been lost but also to check actual bleeding. In acute hemorrhages the results are naturally very brilliant. Hemorrhage occurring in infants and children is usually the symptom of an under-

* Robertson, Bruce; Brown, Alan; Simpson, Ray, Northwest Med., ii, No. 9, p. 233.

† Unger, L. J., Transfusion of Unmodified Blood, An Analysis of 165 Cases, J. A. M. A., lxix (1917), p. 2159; The Therapeutic Aspect of Blood Transfusion, *Ibid.*, lxxiii (1919), p. 815.

lying blood dyscrasia and therefore will be discussed in connection with blood diseases. It may, however, follow an operation or be associated with trauma or typhoid fever.

The supposition has no basis in fact that, owing to the rise in blood pressure following a transfusion, bleeding will increase from vessels which cannot actually be ligated. One transfusion is often sufficient to check gastric or intestinal hemorrhage even though there is active bleeding at the time of the transfusion. The results in such patients are dramatic. They can be converted within a few minutes from moribund individuals to convalescents.

2. Diseases of the Blood.—In secondary anemia the results are often satisfactory especially if the primary cause can be removed. For the anemia associated with malaria, malnutrition or long-continued infections it is very valuable.

In pernicious anemia transfusion yields results superior to any other mode of therapy. Frequently it acts as a life-saving measure by initiating the onset of a remission. There is no evidence, however, that the disease can be permanently cured in this way. Nevertheless by repeated transfusions remissions can be effected and the lives of some patients prolonged for years. When transfusion is successful an increase in strength and appetite is very striking. If the transfusion is repeated because the first one failed to bring about a remission, a different donor should be employed and this procedure should be continued until, if possible, the desired effect is achieved. In such cases repeated transfusions should be resorted to before all the ground that has been gained is lost. In certain cases, however, even this procedure is of no avail. In von Jaksch's anemia or Banti's disease transfusion is merely of temporary value. In lymphatic leukemia only a temporarily favorable effect can be secured by transfusion even though a large amount of blood is withdrawn by phlebotomy and a massive transfusion performed or repeated transfusions are given or transfusions are carried out very early in the disease. Transfusions will raise the hemoglobin, increase the number of red blood cells, diminish the number of white cells (leaving the differential count practically unchanged), lower the temperature, improve the general condition and stop the hemorrhages. Relapses, however, soon occur and the result is invariably fatal.

Hemophilia is not cured by transfusion; but for the bleeding of hemophilia it is practically a specific. Transfusion will succeed when all other measures fail. In almost every case one transfusion will check the hemorrhage. In rare instances two or three transfusions are necessary. If the bleeding is not very profuse, it can occasionally be controlled by subcutaneous injections of horse serum, human serum or human blood. Thromboplastin if applied properly to the bleeding point is often a specific. Valuable time should, however, not be lost if the bleeding is not immediately controlled by these other methods, since we have at our command a specific that will not only check the hemorrhage but also replace lost blood.

Purpura hemorrhagica is a condition that one would expect to be favorably influenced by blood transfusion. The results are, however, only fairly good. In hemophilia usually one transfusion will stop the hemorrhage. In purpura several transfusions are often necessary to control a single attack of bleeding. If in severe cases a series of transfusions are given, it may prove to be a life-saving procedure.

In purpura there is a diminished blood platelet count although approximately a normal amount of blood platelet material is present. This material exists in two forms—platelets that are visible and those that are in solution in the plasma. The manifestations of purpura hemorrhagica are possibly caused by a toxin which not only injures the blood-vessel walls but also dissolves the blood platelets. Since in certain hemolytic diseases the toxin is thought to be associated with the spleen, Hess has suggested that in purpura, after preliminary transfusion, splenectomy be performed. This suggestion gains added force when we remember that following splenectomy there is an increase in blood platelets. Partial destruction of the spleen by Roentgen rays, together with blood transfusions, may also be valuable in some cases. The newer high voltage Roentgen-ray machines which use a 16 in. spark gap almost invariably will shorten the bleeding time (carcinoma patients) and might prove of value in purpura hemorrhagica.

In bleeding of the newborn transfusion is a specific. An almost exsanguinated baby, too weak to cry and in a dying state, is transformed immediately into an apparently healthy, rosy, crying baby. If the bleeding is only external as from the cord or penis, thromboplastin, coagulin, epinephrin or subcutaneous injections of serum or blood may be tried before resorting to a transfusion. When hemorrhage is from the stomach or bowel, temporizing by using less effective measures may cost the baby's life. Internal hemorrhages are more serious because we do not know just when the hemorrhage began or to what extent it has progressed. Just as soon as the diagnosis of bleeding from the stomach or bowel of the newborn is made, transfusion should be performed.

3. Toxemias.—Transfusions have long been used in a limited number of types of toxemias. It is in this group that the indications should be enlarged. For toxemias associated with acute infection, as pneumonia or typhoid fever, transfusion is very effective. This is especially true if there is an associated secondary anemia.

4. Nutritional Disturbances.—In cases of alimentary decomposition and marasmus, transfusion is a valuable adjunct to the recognized treatment. It is not, however, a specific. It will increase the child's tolerance for food. The temperature is less apt to be sub-normal. In some cases there will be an increase in the child's weight. At times blood transfusion in this condition is a life-saving measure. It is especially of value in cases in which there is an associated secondary anemia. By systematically using this mode of therapy the mortality of this condition can be greatly reduced.

In acute intestinal disturbances, transfusion is of value. In these diseases also the mortality can be reduced, especially in cases in which there is an accompanying anemia.

In pyloric stenosis it is useful merely to improve the operative risk or lessen post-operative shock.

For premature infants and difficult feeding cases it is of value to tide the child over the critical period.

5. Shock.—Transfusion is at times valuable in shock. In traumatic and in post-operative shock it is often useful. For shock following burns it should be employed and is of value for the toxemia associated with this condition. The nearer the transfusion approaches the advent of the shock, the more likely it is to be successful. If hemorrhage is associated with shock transfusion is of exceptional value. It should be used preliminary to operations as a supporting measure and thus lessen post-operative mortality.

6. Infection.—In localized pyogenic infections, transfusion will increase the patient's vitality and aid in overcoming infection. In chronic osteomyelitis with associated anemia it is of great value.

In bacteremia transfusion is of exceptional value provided, as Unger* has recently shown, the donor is one who has been immunized with a vaccine prepared from the organism isolated from the patient's blood. The results of transfusion in sepsis when the blood of an ordinary strong, healthy individual is employed are only fair. Normal blood has very little bactericidal effect. If, however, the source of supply of the organism can be shut off, as by ligating the jugular vein in a case of sinus thrombosis, the results with ordinary blood are greatly improved. In some cases, however, a positive blood culture will persist even after otologic operations and transfusions have been performed. Because of the comparatively poor results from transfusions of normal blood in these cases and also in cases in which the source of supply of the organisms cannot be shut off, it is advisable to employ donors who have been immunized by means of a vaccine made from the organism obtained from the blood of the patient. Using this vaccine in the accepted fashion will not immunize a donor—immune bodies will not be developed rapidly in this way. Huge doses of the vaccine must be employed. Daily injections for seven days should be given starting with one billion and rapidly increasing until a total of 150 to 200 billion is reached. In this way, 10 days after the first injection, bacterial agglutinins can be demonstrated in the donor's serum in a titer of about 1 to 60 and his phagocytic index will be greatly increased. The donor selected for this immunization should be one whose blood is not only compatible with that of the patient but also whose phagocytic index is high. A donor who has been prepared for the patient by injecting a vaccine prepared from the organisms isolated from the blood of this patient is an "*autogenous immunized donor.*" If the vaccine used was made from organisms

* Presented before the Otological Section of the N. Y. Academy of Medicine.

obtained from the blood of some other patient the donor is called a "*heterogenous immunized donor.*"

When the diagnosis of bacteremia has been made, the patient should be transfused with the blood of a "heterogenous immunized donor." The patient should be given one, two, or perhaps three transfusions from the "heterogenous immunized donor." By this time the autogenous immunized donor has been prepared and should be used. Transfusions from such a donor should be repeated until the blood culture becomes negative. Usually the temperature persists even after the blood culture is negative. This is due to the formation of abscesses. Their appearance is a favorable prognostic sign. After they have been incised and the pus evacuated the temperature becomes normal.

The perfection of the technique of blood transfusion and the better understanding of its indications marks one of the most useful therapeutic advances in recent years. About 55 per cent. of patients receiving blood transfusions recover from the disease for the cure of which the transfusion was performed. The prognosis in these cases was either very bad and the transfusion was a life-saving measure or the patient was somewhat better, but nevertheless was definitely helped. Blood transfusion is a life-saving measure in about 35 per cent. of the cases. In about 6 per cent. of cases no improvement occurs although from the nature of the disease a good result might have been expected. Occasionally blood transfusion is performed as a measure of last resort although little or no good is expected, and death is due to the underlying disease.

The best results of transfusion are obtained in hemorrhages and diseases of the blood. In about 90 per cent. of cases of acute hemorrhage bleeding can be checked by one transfusion. In pernicious anemia remissions can be initiated. Repeated transfusions frequently bring on repeated remissions. For the hemorrhage of hemophilia and bleeding of the newborn transfusion is a specific. If active bleeding is present delay due to using palliative measures is often dangerous. In purpura hemorrhagica transfusion yields moderately good results. All attempts to influence acute leukemia have failed.

Transfusion yields encouraging results in toxemia associated with acute infections. In nutritional disturbances it is of value especially if there is an associated anemia. It overcomes shock if employed at the onset of the symptoms. Transfusion is of assistance in overcoming chronic suppurative processes. In bacteremia it is often a lifesaving measure. Repeated transfusions must, however, be performed. The blood should be obtained from an "autogenous immunized donor." To tide over the period during which this donor is being prepared transfusions from a "heterogenous immunized donor" should be performed. In this way the bacteremia can frequently be overcome.

CHAPTER LXXX

DISEASES OF THE SPLEEN

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The spleen has long been an object of great interest to clinical and laboratory investigators and theories regarding its function date back to ancient times. Reference to it is frequent in classical literature, there being a widespread belief that it was the seat of various emotions, more especially ill-humor and melancholy. Moreover, the ancients are said to have practiced removal or extirpation of the spleen to improve the endurance of runners and other athletes. Experimental splenectomy was performed on animals as early as the seventeenth century and there are recorded instances of splenectomy performed on human beings for disease of the spleen in the sixteenth century. In spite of these manifestations of an early interest in the organ, our knowledge of its true functions has grown but slowly, and indeed there is much about it that is not clear and remains the subject of controversy.

The spleen is situated in the left hypochondrium, to the left of the stomach and between it and the diaphragm. Ordinarily it is completely hidden behind the costal cartilages, but when enlarged or dislocated downward, its margin can be felt beneath the edge of the ribs. This enlargement may be so pronounced in certain diseases that the lower edge of the organ extends into the pelvis. The spleen is covered externally by a serous coat derived from the peritoneum, and this is reflected on to the vessels at the hilus, helping to support the organ in its proper position. Within this coat is the capsule proper, or fibro-elastic coat, composed of white and yellow elastic fibrous tissue, with a small amount of non-striped muscle fibers. From this capsule, processes or trabeculæ dip down into the substance of the organ to form the supporting framework of the gland pulp.

It has been shown that the spleen undergoes rhythmical contractions and relaxations, due apparently to the contraction and relaxation of the muscle fibers in its capsule and trabeculæ. There is also a slow expansion and contraction synchronous with certain digestive periods: After a meal the spleen increases slightly in size, reaching a maximum at about the fifth hour, and then slowly returning to its previous size. The spleen is richly supplied with nerve fibers (chiefly non-medullated from the celiac plexus) and it is believed that these control the contraction and relaxation of the smooth muscle fibers, perhaps thereby serving to maintain a proper splenic circulation independent of

changes in the general vascular system. (The movements of the spleen have been studied for the most part only in experimental animals, so it is well to remember that most animals have a much greater proportion of muscle fibers in the spleen than is true of human beings, and that in the former the spleen probably shows a greater degree of contraction and expansion than in man.)

Theory of Functions.—During fetal life the spleen is known to possess the power of extensive blood formation, and earlier investigators believed this property continued into adult life. Many recent observers, however, consider it very doubtful that the human spleen under normal conditions is capable of carrying on this function beyond a short period after birth. Under certain pathological conditions, however, a myeloid metaplasia may occur, and the spleen regain its fetal function. Intra-peritoneal injections of splenic extract in the dog, moreover, regularly cause a sharp but temporary increase in the red cells and hemoglobin content of the blood, and, less regularly, in the number of leukocytes (Danilewsky,[1] Pearce[2]). These facts, and the tendency to anemia after splenectomy in normal dogs, would seem to suggest that the spleen may normally exert some stimulating effect on red-bone marrow. Moreover, it is now quite generally conceded that the spleen also has the ability to destroy red blood-cells, this occurring through phagocytosis of the erythrocytes and possibly the liberation by these phagocytic cells of a ferment capable of acting extracellularly. Furthermore, Bottazzi,[3] Banti,[4] and others believe that the erythrocytes, in their passage through the spleen, are acted upon by some unknown substance which makes them more susceptible to hemolysis. The spleen is relatively rich in iron, but whether this is due to a storing up of this substance from tissue and erythrocyte catabolism, or a more direct influence of the spleen upon iron metabolism, is still a moot point. Pearce[5] and his associates from their experiments conclude that the spleen exerts no constant or important influence on iron metabolism and they were unable to show any utilization of iron by the spleen for the manufacture of hemoglobin.

Because chemists at various times have reported the finding of fats, fatty acids, cholesterin and extractives belonging to the purin group in the spleen it has been thought that possibly some active metabolic changes occurred in this organ. Metabolic studies on these points are few, but would seem to indicate that in animals at least, in the absence of anemia, removal of the spleen has no influence upon nitrogen or fat metabolism. In the hemolytic anemias of man, however, according to Pearce,[6] splenectomy is, as a rule, followed by a reduction in the elimination of uric acid, iron and urobilin, changes indicative of decreased destruction of tissue and blood elements, and due in all probability to some factor other than the mere absence of the spleen.

Histologic evidence of the presence in the spleen of large cells which are phagocytic for erythrocytes would suggest the possibility of these cells liberating a ferment or hemolysin which may be capable also

of acting extra-cellularly. It is quite generally admitted that many red blood-cells undergo their final disintegration in the spleen through the action of some hemolytic substance, and that the hemoglobin thus liberated is carried through the portal system directly to the liver where it is changed into bile pigment. Experimental evidence intended to show the existence of such a hemolysin or other ferment has been quite contradictory, and for the present its existence must be considered as lacking of proof.

Relation to Infectious Diseases and Intoxications.—The spleen is apparently concerned in some way with the defensive mechanism of the body against the infectious diseases and various intoxications, and it is found enlarged, congested and even acutely inflamed in many such conditions. Not only do bacteria and their toxins effect such changes, but also certain chemicals, particularly various coal-tar products. Being in such close anatomic relationship to the portal system it has been thought that possibly the spleen filters out some of the toxic products from the blood and thus helps protect the liver. However, it has been demonstrated both on animals and on human beings that splenectomy apparently causes no appreciable or permanent lessening of resistance to the infectious diseases, and the whole problem remains an unsettled one.

Action as Reservoir for Portal Blood.—During the active stage of digestion when the blood in the portal system is greatly increased in quantity, the spleen also increases in size, and because of its anatomic relationship is supposed to act as a reservoir for portal blood. The increased size is apparently due to a vasomotor dilatation of the blood vessels in the spleen with a general relaxation of the musculature in the capsule and trabeculæ The organ's enlargement in those conditions attended by portal stasis (e.g., disease of the heart and liver) may also serve to relieve the strain on the portal system, but such mechanical actions are probably only very subordinate functions of the spleen.

Physiologic Results of Splenectomy.—Removal of the spleen from the body as a cure for disease of the organ, and, in experimental animals, as a method of studying its function, has been practiced since the middle ages. The history of this procedure, as well as much experimental evidence regarding its physiologic results, has recently been gathered together in an excellent monograph by Pearce, Krumbhaar and Frazier. The results of splenectomy in the dog as determined by them may be briefly summarized as follows:

1. An anemia of varying degree, with a decrease in hemoglobin and in the number of red cells, and a well-marked leukocytosis especially in the polymorphonuclear elements. The anemia reaches its severest stage after one and a half months, and is followed by improvement which is well advanced after three or four months, but may not be complete for some months longer. In man, after removal of the spleen for injury or simple lesion not involving a disturbance of function, mild anemia and delayed repair is also the rule.

2. There is an increased resistance of the erythrocytes to hypotonic solutions of sodium chlorid and various hemolytic agents.

3. A lessened tendency to the production of hemoglobinuria and jaundice after the administration of hemolytic agents. This is due partly to the fact that the anemia and increased resistance of the red cells reduces the amount of hemoglobin set free, but mainly because the liberated hemoglobin from the disintegration of erythrocytes now reaches the liver through the general circulation and therefore much more slowly and in more dilute form than normally, through the portal system.

Less frequent results of splenectomy are the destruction of erythrocytes by endothelial cells of the lymph-nodes and the liver and the transformation of the marrow of the long bones from a yellow to the red variety. No influence was noted on nitrogen, fat or iron metabolism

Removal of the normal spleen in the dog is not followed by the so-called "blood crisis" (appearance of "stimulation forms" such as normoblasts, megaloblasts, reticulated erythrocytes, Howell-Jolly bodies and Cabot ring forms) which is so frequent after splenectomy for splenic disease in man.

Congenital Absence of the Spleen.—Further proof that the spleen is not necessary for life is furnished by the occasional reports of the congenital absence of the organ. A little more than a dozen such cases have been reported, the absence of the spleen apparently not causing any recognizable symptoms or appearing in any way to interfere with the normal life of the individual. It is supposed that in such cases any functions the spleen may have are taken over by the lymph-nodes and other blood regulating organs.

Accessory Spleens.—Accessory or supernumerary spleens are not infrequently met with in man, usually as small buds of splenic tissue situated between the peritoneal folds near the hilum, but they may appear in any part of the abdominal cavity. In size they usually range from that of a pea to a walnut, and their number may vary from one or two to several hundred.[7] These must not be confused with the so-called hemolymph glands, which occur in similar situations.

Malformations.—These are quite common, the most frequent being anomalies of the normal splenic notch. This may be unusually deep so that the spleen is almost cut in two, or it may be situated near the lower pole, or rarely, on the posterior border. Again there may be several notches, producing a lobulated appearance. The shape of the spleen may be unusual, as when the organ is unduly elongated, or the normally sharp anterior border is rounded. Occasionally the organ may also show small buds of splenic tissue cropping out from its substance. Rarely it is entirely replaced by a cluster of such buds, or by a number of such small masses scattered about the peritoneal cavity.

Malpositions.—Occasionally the spleen may be found in situations other than the normal, as for instance on the right side of the abdominal cavity (usually as part of a complete situs transversus).

It has also been found in a large umbilical hernia, and, in conjunction with a defect in the diaphragm, in the left thoracic cavity. More commonly, however, the spleen merely drops down slightly from a general relaxation of the ligaments and musculature. This is seen occasionally even in infancy, while in older children it may be a part of a general visceroptosis. Severe thoracic deformities, especially of the rachitic type, may cause a similar downward displacement.

Movable Spleen.—The spleen is supported by ligaments in such a way as to be normally movable within certain narrow limits. Its position alters slightly with the movements of the stomach and with respiration so that the organ moves downward on deep inspiration and upward with expiration. It may also be pushed down somewhat by left-sided pleuritic effusions, or upward by fluid in the abdominal cavity, and by distention of the colon with gas or feces. When unduly mobile, it is referred to as a "movable" or "wandering spleen," and in such conditions may be found in situations far removed from the normal, as for example even in the pelvis. It may change its position with changes in the position of the patient, or may become fixed by adhesions in an abnormal situation, when the term "dislocated spleen" is applied to it. As to the causes of this condition, occasionally a congenital elongation of the supporting ligaments may be responsible, but much more commonly there is a stretching of the ligaments due to an increase in the weight of the organ from some disease. In adults it may be associated with general visceroptosis, but this is rarer in childhood. It is said to occur oftener in malarial spleens than in any other variety. The symptoms produced by the disorder are usually very slight, the chief one being a dragging sensation in the left side of the abdomen, and, occasionally, disturbance in function of the neighboring organs from the traction made upon them by the heavy spleen (nausea, vomiting, epigastric distress). After a time, however, interference with the circulation often produces an engorgement of the spleen, which adds considerably to its weight. This congestion may be increased by torsion or twisting of the pedicle, which, if sudden and marked, can produce symptoms simulating intestinal obstruction (severe local pain and tenderness, abdominal rigidity, splenic enlargement, vomiting, pallor, shock and collapse). If unrelieved, torsion of the pedicle may result in hemorrhage, gangrene or peritonitis.

A movable spleen can usually be differentiated from other abdominal tumors by the size, shape, splenic notch and absence of dulness in the normal position. Furthermore the spleen, unless fixed by adhesions, can ordinarily be pushed back into its former position. The conditions for which it may be mistaken are movable left kidney (with which it is often associated), hydronephrosis and other abdominal tumors, especially those with a pedicle. In the milder cases, no treatment is necessary, or at most only the wearing of a suitable binder or adhesive plaster support. In severer cases operation is indicated, splenectomy being generally preferable to splenopexy, because of the fact that the organ is usually the seat of some disease which renders

less radical measures of doubtful efficacy. Acute strangulation demands immediate operation, but leukemia and amyloid disease are usually considered contra-indications to any surgical procedure.

Congestions and Inflammations of the Spleen.—These will be found discussed under the headings of the various diseases to which the splenic enlargement is usually secondary, but it may be well to consider them as a class at the present time also. No sharp line of demarcation can be drawn between splenic congestion and inflammation, as they are usually due to the same causes, and, representing different stages of the same process, one merges insensibly into the other. When occurring acutely, the designation "acute splenic tumor" is usually used and represents, briefly, active hyperemia of the spleen, with or without inflammatory changes. Acute splenic tumor is seen oftenest as the result of irritation and congestion from microörganisms or their toxins during the course of some acute infection, as for example, typhoid fever, malaria, syphilis, pneumonia, septicemia, etc. Less commonly, a somewhat similar process may be produced by chemical irritants such as ricin, abrin, acetanilid and other coal-tar products. In the earlier stages, the organ appears enlarged, congested, and rather firm. On section, the spleen pulp appears dark red, swollen, and projects above the cut edge of the capsule. The Malpighian corpuscles are usually obscured by the glistening, smeary pulp, while here and there may be visible areas of hemorrhagic extravasation. Microscopically the vessels and spleen pulp are found full of blood and if the process has continued for some time, pigment masses and degenerated corpuscles are also in evidence. As the process progresses the spleen becomes softer, more friable and on section the pulp is found of somewhat lighter color with prominent Malpighian bodies. The capsule may still be tensely distended, or in some cases appears wrinkled as though shrinkage of the organ had occurred with the appearance of more definite inflammatory changes. Microscopically there is now seen a great increase of the cells of the spleen pulp, particularly in the Malpighian bodies, with some hyperplasia also of the other splenic elements. Still later, there may appear marked degenerative changes in the cellular elements of the organ, with pigmentation from disintegration of red cells.

Complete resolution is the rule in acute splenic tumor, but occasionally there is a persistence of the inflammatory process, or the infection is repeated and a chronic inflammatory hyperplasia results, as in the "ague-cake" of malaria. Rupture of the softened spleen, either spontaneous or as the result of trauma is a rare possibility but abscess formation is somewhat commoner. Chronic splenic tumor is seen at times in almost all the chronic diseases of early life, but occurs most frequently in rickets, syphilis, malaria, tuberculosis, the blood diseases, amyloid degeneration, new growth sand the stasis or passive congestion due to portal obstruction. Stasis, as a cause of splenic tumor, acts mechanically by damming back the blood in the splenic vein either as a result of obstruction to the general circulation (as in

diseases of the heart and lungs) or of portal obstruction (from cirrhosis of the liver or pressure from tumors or inflammatory masses). The spleen in all these conditions is usually large, firm, dark in color, with thickened capsule and trabeculæ. There is a hyperplasia of the connective tissue in and about the follicles, as well as in the walls of the small blood-vessels, and an abundance of pigment visible microscopically. Variations in the pathologic picture, such as that in tuberculosis, syphilis, Hodgkin's disease, leukemia and the splenic anemias, will be found described under these diseases.

As splenic enlargement is almost invariably secondary to some other disease, only a brief description of the symptoms produced by it will be attempted here. The only important clinical symptom is enlargement of the organ, occasionally with slight pain and tenderness on pressure. There is often a dragging sensation or feeling of uneasiness in the left hypochondrium, however, which may extend to the epigastrium. Deep breathing accentuates the pain when present, and the latter is apt, both in splenitis and perisplenitis, to be at its height about four to five hours after eating, because at this time the spleen has reached its maximum size, is full of blood, and the tension on the capsule is greatest. In certain instances the pain is referred to the left shoulder or the interscapular space, and there may be pressure effects on neighboring organs (digestive, cardiac, or respiratory disturbances). Mechanical irritation, as in running or jumping, increases the discomfort or initiates it. Secondary symptoms usually depend upon the primary disease, or upon complications (e.g., torsion of the pedicle, infarct, abscess, rupture, etc.). The treatment is, of course, that of the primary disease which has caused the splenic enlargement. If the pain is severe enough to cause distress, relief may be obtained by means of catharsis together with local measures such as the application of heat or cold, blisters, dry cupping, or strapping the side with adhesive to limit the respiratory movements. In chronic enlargement, of doubtful etiology, quinine, the iodides, arsenic and iron have all been thought to be of some occasional benefit, but probably the most effective measure is the very cautious application of the *x*-ray. Splenectomy may also be considered in those cases known not to be due to leukemia or amyloid disease.

Perisplenitis.—Perisplenitis is an acute, subacute or chronic inflammatory process involving the splenic capsule proper, its peritoneal covering, or both. The chief causes of the condition are: (1) Localized splenic involvement (e.g., infarct, hemorrhage, gumma, abscess, cysts, tumors, or trauma); (2) general involvement of the entire organ as in the infectious diseases; (3) by extension of an inflammatory process from outside the spleen, as in pleurisy, pneumonia, peritonitis, tumors, etc. The process may involve the whole covering of the organ, but more commonly is circumscribed or even localized to one or more small patches. All degrees of inflammation are seen, from a mere roughening of the peritoneal surface to the deposit of a thick fibrinous or purulent exudate. Adhesions to

surrounding structures now develop, often with marked thickening of the capsule at these points and scarring of the splenic surface from contraction of the fibrous areas.

The most striking symptom of perisplenitis is pain, varying in intensity from slight discomfort on pressure to great distress. It is intensified by deep breathing and all movements of the body which tend to disturb the position of the spleen (lying upon the left side, bending forward or backward, etc.). Anyone in the habit of frequenting the autopsy room, however, cannot fail to notice the great number of times that dense splenic adhesions are found which were unsuspected during life, because productive of such slight symptoms. On auscultation over the spleen, in acute lesions, fine crepitation or friction sounds may occasionally be heard, a point of considerable diagnostic importance. Careful differentiation must of course be made from inflammatory processes involving the diaphragmatic and lower parietal pleura. Fever may occur with the more extensive lesions of a perisplenitis but often depends on the primary infection or concomitant lesions in other organs.

The **treatment** is directed toward the relief of the pain through local applications or strapping with adhesive, and when necessary, the administration of opium or some other anodyne. Abscess formation about the spleen will of course demand surgical intervention.

Abscess.—Abscess of the spleen, or acute suppurative splenitis, is rarely primary. As a result of its peculiar anatomical construction and sluggish circulation, during pyogenic infectious microörganisms from the blood stream or septic emboli, find ready lodgement in the spleen and furnish the commonest cause of abscess. Thus the spleen may be found the seat of septic emboli originating from an ulcerative endocarditis, cardiac thrombosis, or abscess of the lung, or perhaps of metastatic abscesses occurring during the course of a pyemia or septicemia. Secondary infection may also take place in the infectious diseases, such as typhoid, typhus, malaria, relapsing fever and even tuberculosis and syphilis. Sometimes there is an extension of the inflammatory process in adjacent organs (empyema, peritonitis, subphrenic abscess, etc.).

Metastatic abscesses are usually multiple and small though they may vary in size from microscopic collections of pus to those occupying the greater part of the organ. They are located oftenest near the surface and produce a localized perisplenitis with the formation of adhesions. When septic emboli lodge in the spleen, there is first an anemic infarct formed, which subsequently undergoes suppuration, beginning at the apex of the infarct. Small collections of pus may be absorbed or become inspissated, or even become encapsulated. Larger abscesses may rupture into the peritoneal cavity, pleura, stomach, kidney, and occasionally externally.

Abscess of the spleen is rarely diagnosed during life, though seen quite frequently at autopsy. The reason for this is the absence of characteristic symptoms indicating splenic involvement. As in any

septic process, there may be irregular fever, chills, sweats, leukocytosis, anemia and wasting. Generally, there is pain in the region of the spleen, which is found enlarged and tender to pressure. Pain is usually an indication of a perisplenitis, abscesses well within the parenchyma being ordinarily painless. If the lesion is situated in the upper pole, the pain may suggest a diaphragmatic pleurisy. In abscess caused by a septic embolus, the symptoms are of sudden onset, usually with severe pain in the left side followed by splenic enlargement, tenderness and the signs of suppuration. Unfortunately many of these symptoms are apt to be masked by the symptoms of the primary disease (septicemia, septic endocarditis, etc.). A friction rub, due to perisplenitis, felt or heard over the spleen, may give a valuable clue. Rupture into other organs is recognized by the special symptoms produced. Exploratory puncture of the spleen may occasionally be justifiable, but is a measure which must be used with great caution, because of the danger of death from secondary rupture and hemorrhage. The *x*-ray, however, may in certain instances offer help.

The **prognosis** is always grave but especially so in the embolic and metastatic types where the primary condition in itself usually constitutes a serious menace to life. Once the diagnosis is established, the only **treatment** to be considered is surgical intervention. While the choice of operation must be decided by the surgeon in the individual case, the preference is usually given splenotomy over splenectomy, because of the frequency of adhesions which bind down the organ and make removal difficult.

Infarct.—Owing to the fact that the arterioles in the spleen are "terminal" or "end arteries" infarction of this organ is seen relatively frequently in the autopsy room. Its recognition during life is much rarer. The commonest cause is embolism, arising from cardiac thrombi in the course of an ulcerative or vegetative endocarditis (which in childhood is due usually to the streptococcus viridans). Pyemia is also a frequent cause. Emboli arising from aortic lesions are much rarer in children than in adults, because of the infrequency of aortic disease during childhood. Thrombosis of the branches of the splenic artery or vein may also occur, especially in the specific infectious diseases such as typhoid, or in marantic or anemic states.

When an embolus lodges in a terminal branch of the splenic artery, the circulation in that part of the spleen supplied by this vessel is cut off, and a wedge-shaped, anemic area results. This may remain anemic and undergo coagulation necrosis, with the formation of an "anemic" or "white infarct." In other cases, however, secondary hemorrhage occurs into this area, and a "red" or hemorrhagic infarct results. Infarcts are situated in the peripheral part of the organ, as hard wedge-shaped areas with the base toward the splenic surface and the apex directed toward the site of the embolus. They may be single, or, more commonly, multiple and vary in size according to the size of the artery plugged. Subsequently they become organized and replaced by fibrous tissue, the contraction of which leaves a puckered

scar on the splenic capsule. If the embolus is a septic one, abscess of the spleen usually results. As an infarct usually extends to the surface of the spleen, a localized perisplenitis commonly occurs.

In infarct of the spleen, the most suggestive symptom is sudden pain in the splenic region, occurring during the course of valvular disease of the heart, pyemia, or other conditions which are apt to provoke embolism. Pain is often quite severe, but may be slight or even absent. In some cases it lasts for only a day, but usually the secondary persiplenitis causes the tenderness and pain to persist for several days, or even weeks. The pain is usually aggravated by movement and deep breathing, and occasionally a friction rub can be felt over the spleen. Irregular fever and chilliness may indicate a septic process with possible abscess formation but often these symptoms are masked by the primary disease causing the embolism.

The **prognosis** in those cases caused by non-infective emboli is usually good. In other cases it is influenced by the primary disease and whether or not splenic abscess results. The **treatment** is directed toward relieving the pain by means of local applications of heat or cold, blisters or dry cupping. Strapping the side with adhesive often produces relief by limiting the respiratory movements. In severe cases, opium or its derivatives must be used.

Rupture of Spleen.—Rupture of the spleen may be either spontaneous (in disease of the organ) or the result of trauma. Protected as it is by the ribs, it requires crushing injuries or other severe trauma to cause rupture of a previously healthy spleen, but even slight trauma (such as coughing or other strain) can cause rupture in a spleen which is already the seat of a pathologic lesion. Excessive enlargement of the organ and stretching of the capsule predispose to the condition, as do soft friable splenic pulp and lesions of the capsule. Spontaneous rupture of the spleen occurs oftener in malaria (especially in tropical countries) than in any other disease, but has been observed occasionally in the other infectious diseases, such as typhoid, relapsing fever, tuberculosis, etc., as well. Infarct and abscess of the spleen, or disease of the splenic vessels, are less frequent causes. The extent, depth and situation of the laceration determine the amount of hemorrhage, which in most cases is very profuse. In rare instances, the hemorrhage is entirely beneath the capsule, or limited by adhesions about the spleen.

Symptoms.—The most striking symptoms of rupture of the spleen are sudden severe pain in the splenic region, followed by collapse and signs of internal hemorrhage. The pain does not always follow immediately after the injury, and the patients may even walk some distance from the scene of the injury before complaining. The pain is accompanied by a sensation as of something having torn loose or given way in the region of the spleen, to be followed by signs of internal hemorrhage (pallor, faintness, rapid thready pulse, nausea, cold extremities, subnormal temperature, sighing respiration and dilated pupils). There is a rapid distention of the abdomen, with shifting dulness in the left

flank, or on both sides. If the size of the spleen before rupture is known, diminution in size may be a valuable symptom. Secondary peritonitis may develop, especially if the organ is the seat of some septic process.

The **diagnosis** is apt to be suggested by the history of any injury, but positive diagnosis may be impossible in those cases with only slight hemorrhage. Rupture of a cyst or abscess may present a somewhat similar picture, except that in these instances the signs of internal hemorrhage are not so pronounced. Differentiation from other varieties of internal hemorrhage may be impossible but this is not very important, as these likewise call for prompt surgical intervention.

Prognosis.—This is always grave, as usually hemorrhage is so profuse as to cause death, unless surgical aid is immediately available.

Treatment.—The treatment is immediate operation.

Thrombosis of the Splenic Vein.—Etiology.—Thrombosis of the splenic vein may result from any inflammatory or degenerative process of the vessel wall. Thrombosis, embolism, and atheromatous changes are much rarer in children than in adults, but such cases have been described at almost all ages. Thrombosis is occasionally seen in the infectious diseases, especially in diphtheria, or less frequently typhoid fever, and in young children with severe wasting disease (cachectic or marantic thrombosis). It may also be caused by pressure from a tumor (e.g. new growths of the kidney, large masses of tuberculous lymph-nodes), trauma, torsion of the splenic vein in movable spleen, extension of a thrombotic process in the portal vein or splenic radicles, etc. Thrombosis may likewise occur from extension of a suppurative pylephlebitis, depending upon some focus of infection in the umbilical vein or some part of the abdomen from which the branches of the portal vein arise.

Pathology.—Thrombosis of the splenic vein results in a more or less complete obliteration of the vein, with congestion and enlargement of the spleen from venous obstruction. If the intrasplenic radicles are completely occluded hemorrhagic infarction results. As a result of the chronic congestion of the spleen, there is an increase of connective tissue and more or less fibrosis develops. Occasionally, calcification of thrombi gives rise to the formation of so-called "splenic stones."

Symptoms.—These are directly referable to the mechanical effects of the venous obstruction. There is enlargement of the spleen with disturbance of its function as well as that of neighboring organs. There is a marked tendency to hemorrhage particularly from the stomach, and in general the clinical picture cannot be differentiated from that of one of the splenic anemias. Indeed, in the latter condition obstruction of the veins of the portal system, especially the splenic and portal veins, has been noted quite frequently.[8]

Treatment.—The treatment is similar to that employed in splenic anemia. Splenectomy should be done in those cases with recurring hemorrhages or where there is no benefit from other measures.

Amyloid Spleen.—Amyloid disease is the name applied to a condition in which infiltration of certain organs with amyloid substance occurs. The term "amyloid" was applied by Virchow because certain staining reactions given by the substance suggested a similarity to starch. It is in reality, however, probably a glycoprotein, apparently a combination of chondroitin sulphuric acid with a protein.

The disease is rare in infancy, but commoner in older children, though much less frequent during the entire period of childhood than in later life. It may affect a number of organs, chiefly the spleen, kidney, liver, blood-vessels and intestinal mucosa. The spleen is affected oftener than any other organ and rarely escapes if amyloid deposits are found elsewhere in the body. Although formerly considered a type of cell degeneration, amyloid disease is now generally classified as an infiltrative process.

Etiology.—Amyloid deposits are found in the spleen usually as a result of prolonged suppuration in chronic joint or bone disease (osteomyelitis), empyema, tuberculosis, and less frequently, syphilis. Occasionally, however, the condition may be met with in other chronic cachexias, as in nephritis, leukemia, and malaria. Amyloid deposits have also been found in the livers and spleens of horses repeatedly injected with diphtheria toxin, as in the preparation of anti-diphtheritic serum.[9] The possibility of its occurrence in human beings following an attack of diphtheria must therefore be borne in mind, although apparently no such cases have been reported in the literature to date. During childhood, perhaps its commonest incidence is in connection with tuberculosis of the spine and hip, particularly if there is much suppuration, and infection by a secondary organism. The underlying chemical or metabolic processes involved in causing the deposit of amyloid material are as yet not understood.

Pathology.—Amyloid disease of the spleen occurs generally in one of two forms, the one affecting chiefly the Malpighian bodies, and the other the parenchyma of the organ. In the former, which is the commoner type, the process begins in the Malpighian bodies, affecting both the blood-vessels and lymphoid elements. On section, the Malpighian bodies appear as small round translucent or waxy areas which resemble boiled sago, and hence the name "sago spleen" has been applied to this type. Sago spleen is usually of normal size or is only slightly enlarged. In the other variety, there is a more uniform involvement of the whole organ, which on section has a translucent, waxy appearance ("bacon spleen"). In the latter variety, while the spleen may at first be rather soft and flabby, it later becomes firm and considerably enlarged, and may reach enormous proportions. There are usually evidences of fibrosis in the organ, and often areas of perisplenitis.

Symptoms.—The symptoms of amyloid or lardaceous disease of the spleen are in no way characteristic. Perhaps the most striking feature is the waxy cachexia, with an alabaster-like appearance of the face, and translucent skin. If the spleen is much enlarged, its size may

cause pressure symptoms and disturbance of function in neighboring organs, but pain and tenderness are rare. The sago spleen, which is the type commonly found, is, however, not very large, and its presence is usually not suspected until autopsy. Other symptoms, such as anemia of varying degree, are largely the result of the primary disease, to which the amyloid condition is secondary. Amyloid changes take place very slowly, during the course of many months or even years, the patients usually becoming steadily worse until they finally die of asthenia or some intercurrent affection. Occasionally the disease seems to be arrested and may remain stationary for long periods.

The **prognosis** is always bad, although arrest of the process, or even cure, has been reported where the suppurating focus could be removed. It is probably not the amyloid disease *per se*, which makes the prognosis so grave but the underlying condition which has given rise to the lardaceous process.

Treatment.—The amyloid changes in the spleen and other organs are usually not amenable to treatment. However, the primary disease on which the amyloid process depends should, of course, be treated; and this often results in an arrest of the secondary destructive processes, which may not be severe enough to interfere materially with life. Thus syphilis can usually be greatly improved by means of proper treatment, chronic suppurative processes and bone tuberculosis are often amenable to successful surgical and hygienic measures. General hygienic and tonic treatment are also indicated for the anemia and other special symptoms.

Enlargement of the Spleen.—Owing to its anatomic peculiarities and unique reaction to infections, the spleen is enlarged in a great many widely different affections. Most of these conditions will be found discussed under the diseases to which the splenic enlargement is secondary, but it may be profitable to consider them briefly as a group at this point also.

Acute Infectious Diseases.—During the period of childhood the spleen has at times been found enlarged in practically all of the acute infectious disorders, even in such mild diseases as rubella and varicella. The changes in the spleen are those characteristic of acute splenic tumor, namely, active hyperemia as the initial stage, followed later by active hyperplasia of the splenic pulp and Malpighian bodies. Under these changes the spleen becomes more or less enlarged, softer and more friable, and on section is of a dark-red color with prominent Malpighian bodies. In other cases the pulp is so swollen as partly to obscure the latter. The diseases in which this acute enlargement is most marked and persistent are typhoid fever, malaria, septicemia, acute tuberculosis, typhus, and relapsing fever. The enlargement is less marked in pneumonia, scarlet fever, measles, influenza, smallpox and persistent intestinal infections.

Typhoid.—In typhoid, enlargement of the spleen is one of the most persistent and characteristic symptoms. The enlargement has usually progressed sufficiently by the end of the first week of the disease

to make the organ palpable beneath the costal border. Ordinarily it does not extend more than 1 to 1½ in. below the ribs, but occasionally it may become considerably larger than this. It recedes with convalescence, and persistent enlargement suggests the possibility of a relapse. The typhoid spleen is soft, friable, and of a deep-red color from the great abundance of red blood-cells in the swollen pulp. The latter often obscures the Malpighian bodies. Areas of necrosis may occur, exactly as they do in the lymph glands and Peyer's patches. The typhoid spleen differs from that found in other infections in the greater abundance of red blood-cells and profusion of large phagocytic cells which are seen engulfing the red cells and other debris. Rupture of the spleen occasionally occurs in older individuals, but is exceedingly rare in children.

Sepsis.—In the various forms of septicemia, the spleen is quite uniformly enlarged, and easily palpable beneath the costal margin. The capsule is tense, but the organ is very soft, and on section has a velvety or pasty appearance with a dull, pinkish-gray color. Usually the swollen pulp obscures the Malpighian corpuscles but, on the other hand, in some cases the chief change appears to be in these bodies and they are accordingly unusually prominent.

Acute Tuberculosis.—Acute generalized tuberculosis often runs a course comparable to typhoid fever, and in such instances tubercle bacilli invade the spleen in great numbers, with profound alteration in its structure. The spleen is enlarged and more or less thickly strewn with miliary tubercles, some of which may be so small as to be invisible to the naked eye. If the disease is very acute, the organ may bear a striking resemblance to a typhoid spleen, being soft and diffluent, of a deep-red color, and microscopically showing intense congestion and even abundant phagocytosis of red blood-cells. Tubercles are numerous, and may entirely replace many Malpighian corpuscles. Such a spleen enlarges very rapidly and its tuberculous nature is often overlooked.

Chronic Enlargements. (a) **von Jaksch's Anemia, Pseudoleukemic Anemia of Infancy.**—This disease, first described by von Jaksch in 1889, is by most authorities on diseases of the blood no longer considered a distinct clinical entity in itself, but rather the infantile form of one of the other blood disorders. It usually appears at the end of the first, or during the second year of life and is generally associated with marked rickets. Its main features are a high-grade anemia with diminution of hemoglobin and red cells, inequality of size and shape in the erythrocytes and the appearance of nucleated forms. Leukocytosis is present, involving either the polymorphonuclear or mononuclear elements. The spleen is enlarged, sometimes enormously so, and there is at times a concomitant, moderate enlargement of the liver and lymphatic glands. The disease will be found more fully described on page 583.

(b) **Leukemia.**—Leukemia is a disease of the blood-forming organs (spleen, lymph glands and bone-marrow), which is infrequent in child-

hood but may occur at any age, even in infancy. The cause of the disease is unknown. In the lymphatic variety, the most striking change is in the lymphatic glands and lymphoid tissue throughout the body. Thus there may be enlargement of the axillary, cervical, inguinal and other glands, due mostly to hyperplasia and infiltration by lymphoid cells. Liver and spleen are also enlarged, chiefly from infiltration by lymphoid tissue, and while the latter organ is often quite large, in lymphatic leukemia the changes in the marrow and spleen may be relatively slight. In the splenomyelogenous form of the disease, however, the spleen is usually enormously enlarged, and the changes in the bone-marrow are very marked. The disease may run a very acute or chronic course, the more frequent type in young children being perhaps the acute lymphatic variety, usually fatal within a few weeks after the onset of symptoms. The diagnosis is ordinarily easily made by an examination of the blood, the characteristic features in the lymphatic variety being a great relative increase in the lymphocytes with corresponding decrease in the polymorphonuclears. The total leukocyte count is usually much increased, but may be normal or below. In the splenomyelogenous variety, however, there is usually an enormous increase in the total leukocytes, with the presence of myelocytes, nucleated reds and other abnormal cells. Leukemia and the affections allied to it will be found discussed in Chapter LXXVII.

(c) **Hodgkin's Disease (Lymphadenoma).**—This is a rare disease which is almost unknown in infancy, but is found with increasing frequency in later childhood. Its etiology has not been determined as yet although several organisms have been described as bearing a causal relationship to the disease. It is of gradual onset and produces a marked enlargement of the lymph-nodes, affecting the cervical group first, as a rule, but later extending to other groups throughout the body. The spleen is usually markedly enlarged, but not to the extent found in leukemia. The liver is less frequently involved. On section, the spleen shows irregular mottling due to the accumulation of the lymphomatous masses throughout the organ. Microscopically there is found here, as well as in the lymph glands, an increase in the lymphoid tissue, and later a proliferation of endothelial and connective tissue, with the formation of giant cells. Eosinophile cells are sometimes found in the tissues in great numbers. The disease at first produces very little disability, but later runs an irregular febrile course with an increasing secondary anemia, and pressure symptoms from the enlarged glands. The blood in the later stages usually shows a polymorphonuclear leukocytosis and an increase in the platelets and transitionals, with occasionally an increase in eosinophiles also. The course of the disease is essentially chronic, and practically invariably ends in death.

(d) **Chronic Venous Congestion.**—This is a common cause of enlargement of the spleen. It is seen very frequently in congenital and acquired cardiac disease with obstruction to the general venous circula-

tion and a damming back of blood in the portal system. The portal vein and its branches (including the splenic vein) being devoid of valves, conditions are very favorable for the production of passive congestion in the spleen. A similar condition may exist in certain pulmonary diseases, such as chronic interstitial pneumonia, chronic pleurisy, emphysema, atelectasis. Obstruction to the portal circulation with passive congestion and enlargement of the spleen may also occur in cirrhosis of the liver, pylephlebitis, or from the pressure of tumors, adhesions, etc. Such a stasis spleen is hard and smooth, with rounded edges, and on section, if the condition has lasted some time, shows a chronic indurative splenitis, with an increase of connective tissue. Infarction is not uncommon. Associated with the enlarged spleen there is often ascites, and signs of chronic passive congestion in other organs.

(e) **Hepatic Cirrhosis.**—Cirrhosis of the liver is much rarer in children than in adults, but as stated in the preceding paragraph, may occasionally be a cause of chronic splenic enlargement. This is produced largely, if not entirely, through obstruction to the portal circulation and passive congestion of the spleen. The etiology of hepatic cirrhosis is in most cases obscure, but syphilis, alcoholism and tuberculosis may be factors in its causation, and possibly some of the acute infectious diseases. The symptoms, which are discussed more fully elsewhere, are in the main similar to those seen in adults, but ordinarily run a shorter and more acute course.

(f) **Splenic Enlargement in Other Forms of Hepatic Disease.**—Other forms of hepatic disease in which splenic enlargement may occur are congenital obliteration of the bile ducts, and both the obstructive and infectious types of jaundice. Congenital obliteration of the bile ducts is a rare condition in which the spleen is quite uniformly found enlarged. The condition, if complete, is, of course, invariably fatal. An enlarged spleen is also found at times in obstructive jaundice. The latter may be due in very rare instances to gall stones, plugging of the hepatic duct with worms, especially ascaris, or pressure from a tumor or packet of enlarged glands. Gastro-duodenitis is said to cause an obstructive jaundice at times, through swelling of the intestinal mucosa and blocking of the common bile duct, but probably most of these cases belong more properly in the class of infectious jaundice. Cases of infectious jaundice may occur singly, often during the course of one of the other infectious diseases, or in epidemic form. In the severest instances, fortunately rare in childhood, there may be chills, high fever, intense icterus, moderately enlarged spleen, hemorrhages and death in convulsions or coma.

(g) **Banti's Disease.**—This is one of the type of so-called "splenic anemias" with splenomegaly and hepatic cirrhosis. The etiology is unknown. The onset is rare before the tenth year, and the first symptoms are usually those of anemia of the secondary type. The spleen is large and firm but there are no distinctive pathologic changes other than fibrosis and hyperplasia. It shows slow but progressive

enlargement. Later the liver enlarges, to be followed by shrinkage of the organ and the production of ascites, and often icterus. There is a tendency to visceral hemorrhages throughout the disease, most marked during the stage of hepatic cirrhosis. Increased excretion of urobilin occurs, indicative of increased blood destruction, but the resistance of the red cells is unchanged, and signs of bone-marrow regeneration (nucleated and reticulated red cells) are slight or absent. The disease is very chronic in its course, and is often terminated by some intercurrent affection. It is one of the diseases in which splenectomy is sometimes of great benefit. Banti's disease is more fully considered on page 543.

(h) **Gaucher's Disease.**—This rare disease is often classified with the so-called splenic anemias but its pathology is so distinctive as to demand its recognition as a definite clinical entity. Originally classified as an epithelioma by Gaucher, it was shown later to lack most of the characteristics of malignancy, and its etiology is still in doubt. The distinctive pathologic feature is the occurrence of characteristic large vesicular cells with small eccentric nuclei, occurring in great abundance in the spleen, liver and, to a lesser extent, in the bone-marrow and lymph-nodes. The disease begins in infancy or childhood, and pursues a very chronic course. Often there is a history of one or more other cases in the family. The most striking feature is a slow, progressive enlargement of the spleen, and slighter enlargement of the liver. There is a moderate anemia of the chlorotic type, with leukopenia and a tendency to hemorrhages, as in Banti's disease, though this is not as prominent a feature as in the latter disease. There is often a brownish discoloration of the skin, especially of the face, and a wedge-shaped thickening of the bulbar conjunctivæ has been noted. The spleen may reach enormous proportions, but the lymph glands are not materially increased in size. In a case seen at the St. Louis Children's Hospital, great benefit was (apparently) derived from splenectomy, although this procedure would not seem to offer hope of a permanent cure in a disease whose lesions are as widespread as this one.

(i) **Tuberculosis.**—Besides the acute form of tuberculosis of the spleen previously mentioned, there is a commoner, more chronic type. The enlargement in this variety is due mainly to the presence of tubercles occurring for the most part as the miliary variety, but not infrequently as larger caseous masses, the latter occurring much more frequently in children than in adults. A localized tuberculosis of the spleen has been described, curable by splenectomy, in which this organ acts as a focus of dissemination of the tubercle bacilli (Winternitz[8]). Such a process, limited almost entirely to the spleen, is very rare. Thursfield[9] states that "clinically an enlarged spleen is more often found in tuberculosis than in any other disease to which children are liable, and in the writer's experience, is the only disease in which the splenic tumor is often distinctly tender to palpation." According to Reinhold (autopsy statistics quoted by Winternitz), of 428 cases of tuberculosis

in children between the ages of 0 to 15 years, the spleen was affected 280 times, that is, in about two-thirds of the cases.

(j) **Syphilis.**—Diffuse hyperplasia of the spleen is a very frequent, almost a constant, finding in hereditary syphilis, and in infants with active symptoms the spleen is palpable in fully four-fifths of the cases. The enlargement is ordinarily not pronounced, the organ usually extending ½ to 2 in. below the costal margin. More rarely, the spleen is the seat of syphilitic gummata, usually multiple and varying greatly in size. Gummata are more apt to occur in the "late" form of hereditary syphilis, and it is in this variety that the spleen occasionally reaches enormous proportions, filling in the whole left side of the abdomen. When this occurs, there is usually marked enlargement of the liver also, with the formation of gummata. In a small proportion of cases, amyloid changes may be found in a syphilitic spleen.

(k) **Rickets.**—The spleen is frequently found palpable in children suffering from rickets. In many cases this is due to downward displacement of the organ from rachitic deformities of the thorax. In other cases, the organ is actually enlarged, due usually to a simple hyperplasia, but whether or not this is due to the rickets *per se*, or the accompanying anemia with associated blood changes, has not as yet been satisfactorily determined. Occasionally with severe anemia of the type referred to under "von Jaksch anemia" the enlargement of the spleen may reach enormous proportions.

(l) **Lardaceous Disease.**—Under the head of chronic enlargements of the spleen it is necessary to mention the comparatively rare instances in which the spleen is the seat of amyloid deposits, usually as a secondary result of prolonged suppurative processes, tuberculosis, or syphilis. These will be found discussed somewhat more fully in the chapter on "amyloid spleen" (p. 647).

(m) **Congenital Acholuric Jaundice (Hemolytic Jaundice).**—This is a type of jaundice which is usually hereditary and often affects several children in the same family. There are two types of the disease, one present at birth or soon afterwards, and the other appearing in later childhood or adult life. The jaundice, which is always present, varies in degree, but is never intense, and is of the non-obstructive type, with bile pigment in the blood serum but not in the urine. A moderate grade of anemia is present, and the spleen is markedly enlarged, hard and firm. Increased elimination of urobilin in the urine and feces points to excessive destruction of red blood-cells, whereas efforts at regeneration of the blood are indicated by the occasional presence of nucleated reds, and a marked increase in reticulated red cells as shown by vital staining methods. Another very characteristic feature of the disease is the increased fragility of the red cells to hypotonic salt solutions and other hemolytic agents.

Histologic examination of the enlarged spleen has failed to reveal any changes except congestion and diffuse hyperplasia. However, splenectomy has produced perhaps its most brilliant results in this disease, usually bringing about marked improvement and even appar-

ent cures. (Hemolytic jaundice will be found considered more fully elsewhere in this work.)

(n) **Status Lymphaticus.**—In this condition, described in considerably more detail elsewhere, there exists enlargement and hyperplasia of the thymus gland, as well as of the lymphatic tissue generally throughout the body. Moderate enlargement of the spleen is common. Children with this affection are usually large, well nourished, and of a rather pasty appearance. Attacks of respiratory difficulty and the liability to sudden death make the condition one of considerable importance.

(o) **Kala-azar.**—Kala-azar, or tropical splenomegaly, is an infectious disease which is rarely seen outside of certain tropical countries. It is characterized by marked anemia, emaciation, prostration, irregular fever, great enlargement of the spleen and occasional ulcerative lesions of the skin and mucous membranes. The disease is due to a protozoan organism, Leischmania donovani, which is found in the blood, spleen, and many other organs of the body. The splenic enlargement appears to be due to a simple hyperplasia. Kala-azar will be found more fully described elsewhere in this work.

Tumors of the Spleen.—Primary tumors of the spleen are exceedingly rare, and even secondary or metastic new growths are much less frequent in the spleen than in other organs. Of the benign tumors, **fibroma, lymphangioma** and **angioma cavernosum** have been described. Fibromata occur as small round nodules, often multiple but causing no symptoms. Angioma cavernosum, which is somewhat commoner than the other two varieties, may reach a very large size, producing a chronic ascites with bloody fluid in the peritoneal cavity. Among the malignant tumors, sarcoma is the commonest, though also very rare. Sarcomata are often multiple, and may be felt as irregular nodules on a greatly enlarged spleen.

Cysts.—Cysts of the spleen are considerably more common than neoplasms. They are usually classified as *simple*, *dermoid*, or *parasitic*.

Simple Cysts.—These are divided into serous, hemorrhagic, or lymph cysts, according to the nature of the contents. They are comparatively rare, and their etiology is often unknown. Some are apparently the result of a localized degeneration of splenic tissue, while others result from trauma and the conversion of a hematoma into a cyst. Often a serous or lymph cyst is changed into the hemorrhagic variety by secondary hemorrhage into it, and this process may be repeated several times. Simple cysts may be either unilocular or multilocular and their size and number varies greatly. Occasionally they may reach such a great size as to cause marked abdominal enlargement and a downward dislocation of the whole organ. Often the walls are very thick, and the mass may be bound down by numerous perisplenic adhesions.

Dermoid cysts are exceedingly rare, and only a few cases have been reported. They can only be recognized by an examination of their contents.

Parasitic Cysts.—Parasitic cysts are the commonest forms met with in the spleen. The only important variety is the hydatid or echinococcus cyst, which involves the spleen in about 3.5 per cent. of the cases of hydatid disease. Hydatid cysts are unilocular and usually single. They may attain a very large size. Occasionally they develop in the tissues adjoining the spleen, and involve the spleen by extension.

Symptoms and Diagnosis.—Benign tumors and cysts of the spleen ordinarily produce no symptoms unless they have attained a considerable size. When large, they may produce pressure symptoms referable to the digestive, urinary or respiratory apparatus, and in addition, there may be a sense of fulness, or soreness over the mass. Occasionally, traction produces referred pain to the left axilla and shoulder. The tumor may usually be definitely localized in the spleen by means of palpation, and the fact that the mass moves with respiration. When the tumor is of the cystic variety palpation and the occasional presence of a fluid wave may aid in determining this fact. Hydatid cysts can be differentiated from simple cysts only by the finding of hooklets, scolices, lamellated membrane, etc., in the fluid. (In this connection it should be mentioned that exploratory puncture for purposes of diagnosis has been followed by very serious symptoms such as toxemia, peritonitis, dissemination of the hydatid disease, etc.). Concomitant cysts of the liver and spleen would speak for a common etiology, usually hydatid disease. Hydatid fremitus over the mass may occur, but is inconstant and unreliable.

Sarcoma usually produces rapid enlargement of the spleen and an increasing cachexia. Frequently the sarcomatous nodules can be felt on the splenic surface.

Angiomata occasionally give rise to pulsation, and this furnishes a clew as to the nature of the mass.

In the differential diagnosis, splenic tumors and cysts must be differentiated especially from tumors and cysts of the left kidney, hydronephrosis and ovarian cysts, as well as from the other forms of splenic enlargement previously described.

Treatment.—The only treatment to be considered is surgical intervention.

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NOTE.—In addition to the above references, an excellent discussion of diseases of the spleen by I. P. Lyon will be found in Osler-McCrae's "Modern Medicine," 2nd Ed., Philadelphia, Lea and Febiger (1915).

A very extensive bibliography is appended to the monograph by Pearce, Krumbhaar, and Frazier, on "The Spleen and Anemia," Philadelphia, J. B. Lippincott Company (1918).

CHAPTER LXXXI

THE THYMUS

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Anatomy.—Despite the very considerable amount of work which has been done on the thymus in the last decade, both in the line of clinical investigation and experimental research, there is as yet no unanimity of opinion regarding its place in the body economy.

Its anatomic status is not fixed, its physiology is not clearly determined. In the light of recent work, it may not even be claimed with certainty that the thymus belongs to the group of ductless glands.

One group of investigators holds that the thymus is absolutely essential to growth and development; another group offers strong testimony that its removal is fraught with no danger whatever to the organism, and that no developmental changes follow its removal in early life.

Definite proof of internal secretion of the thymus has indeed not been offered.

Yet certain diseases of the gland are common and of far-reaching importance. Their clinical importance is thus great and demands careful study.

The thymus is a paired organ of epithelial origin arising from the third and fourth branchial clefts. The two lobes of the gland are formed by extension of the original epithelial diverticula down the sides of the trachea toward the pericardium. At their lower ends these diverticula expand and fuse together. During later growth and development the epithelial structure is invaded by lymphocytes from the adjacent mesenchyme. This lymphoid tissue proliferates, extending between the epithelial elements and later comes to form the bulk of the thymus tissue. The epithelial component persists, however, as the reticulum. Various retrograde changes occur in this epithelial structure until the vestigial remains form the peculiar connective Hassall corpuscles which so prominently identify the gland. The genesis and nature of the small thymus cells has been much discussed. On the whole it seems to be assumed that these small thymus cells are true lymphocytes, and it seems certain that the thymus is a lymphoepithelial organ in which two types of structure coexist in the most intimate (and probably purposeful) relationship (Pappenheimer). One argument in support of the lymphoid nature of the small thymus cells is the fact that one effect of the x-ray on the thymus is the disintegration of these cells. During this process lymphocytolytic substances

are formed which if injected peritoneally into other animals cause lysis of the lymphocytes in the appendix and mesenteric lymph-nodes (Rudberg).

The microscopic features of the gland are an investing fibrous capsule, connective tissue trabeculæ, cortex of lymphoid tissue and a medullary portion containing the Hassall's corpuscles and many eosinophil cells (Warthin).

There is no doubt that the weight of the thymus varies greatly in different individuals at birth, and there is little doubt that considerable variation may occur within normal limits. Warthin agrees with Dudgeon that the weights as commonly given are too high. He finds that from birth up to two years the average weight of the gland is from 7 to 10 gm. Glands of 20 to 30 gm. in the first year of life must thus be considered hyperplastic. The fullest development of the gland is reached at two years, according to some authors, while others believe there is progressive growth up to puberty. Certain it is that involution of the gland proceeds very rapidly after puberty, except in cases of persistent thymus. Vestigial remains of the gland are, however, present in adult life. The thymus then is represented by a mass of fat and fibrous tissue, the so-called thymic fat-body. Enmeshed in this reticulum small nodules of lymphoid tissue containing Hassall's corpuscles are found, which persist even to senility. Therefore, the presence of some healthy gland tissue in adult life or old age may not be interpreted as abnormal persistence or hyperplasia.

Recent researches have shown that the thymus is affected by various infections, and by conditions disturbing the general nutrition of the body. In acute diseases, the specific exanthemata, pneumonia, acute nephritis, and starvation there occurs a pathologic involution which may not persist. Thus in the course of one of the acute infectious diseases the thymus may temporarily be reduced to one-fifth or one-sixth of its normal size.

But some disorders such as congenital syphilis and tuberculosis may produce permanent atrophy or sclerotic degeneration. And herein may lie one explanation of the different sizes ascribed to the gland by various observers.

Dustin has recently shown that the thymus is rarely atrophic in soldiers of 19 to 34 who have succumbed to wounds, and believes that the gland may remain functionally active to a relatively high age.

Physiology.—The same divergence of views that obtains with reference to the anatomy of the gland is found in the recent voluminous literature concerning its physiology. It may be stated at once that the definite function of the gland has not been absolutely determined. One may go further and say that definite proof that the thymus must be classed a ductless gland of internal secretion has not been forthcoming.

E. R. Hoskins closes a critical summary of existing views with reference to the function of the thymus with the following significant statement: "Whatever be the real function of the thymus, certain

it is that its production of an internal secretion has not been proven. The evidence in favor of such a theory is but circumstantial at best and very meager. It is equally difficult to prove that the thymus does not produce a secretion, but the burden of proof is upon those who support the former theory. A statement is not true because it cannot be proven untrue."

As would naturally be supposed, one line of investigation to determine thymus function would be to extirpate the gland in very early life in lower animals, and then study the animals from the viewpoint of developmental anomalies. Various observers have used this method on different species of animals, and their reports are most divergent.

Thus Vincent showed that complete thymectomy on frogs was not fatal, but the animals seemed less resistant to infection. Allen has recently shown that removal of the thymus anlage on frog larvæ caused no deviation from normal development. The larvæ grew normally and metamorphosed at the normal time.

In higher animals thymectomy has been performed under all sorts of conditions with the most contradictory results.

In 1910 Klose and Vogt removed the thymus from a series of young puppies with proper control. The animals operated upon showed various developmental changes uniformly, three distinct stages being noted. First stage marked adiposity with polyphogia, second stage loss of muscular activity, third stage rapid loss of weight and strength with marked rachitic changes in the skeletal system, marked disturbance of the central nervous system, and the development of a cachexia thymipriva. Six years later Tongu reported a very extensive, carefully controlled series of similar experiments. He found no change in the body-weight, he did not see the three stages of change, there was no effect on the central nervous system, no change in the blood corpuscles, none in the opsonic index, no skeletal changes. Histologically there were generally small patches of thymus cells found, due either to regeneration or to the persistence of accessory thymi. No changes macroscopically or microscopically were found in any of the other internal secreting organs, in epithelial or lymphoid tissue. His work offers strong presumptive evidence that the thymus is not an organ of internal secretion.

Park, repeating the experiments in guinea pigs, was unable to discover any of the series of changes as reported by Klose and Vogt. Paton and Goodall removed thymus and spleen in guinea pigs simultaneously, without effect on nutrition, growth or development. The operation was, however, followed by a decrease in the number of circulating leukocytes.

In 1918 Barbara published an extensive monograph on the pathologic physiology of thyroid and thymus in relation to infections. He detailed the results of a series of studies on thymectomized guinea pigs as regards phagocytic power of the leukocytes and complementary, opsonic, and agglutinating power of the blood serum. He believes that

substances originate in the thymus which stimulate phagocytosis. These substances can be demonstrated in extracts from the gland. He believes that thymectomy results in a loss of balance among the defensive mechanisms of the body. But he finds that, after a time, compensating changes take place in other body structures to restore the balance.

Various other observers have reported that thymectomy appears to lower the resistance of the animal to infection.

Calzolari, Henderson, Paton and others have found that there is some sort of relationship between the thymus and the sexual organs. Castration would seem to delay the involution of the thymus, and might even cause thymic hypertrophy. On the other hand, after thymectomy there is often a hypertrophy of the gonads. According to Hoskins a definite relationship has, however, not been proved as yet.

A second line of investigation into the function of the thymus has been the administration of varying quantities of thymus tissue or extracts.

Gudernatsch fed thymus to frog larvæ and found that their metamorphosis was delayed. His results were verified at least in part by Romeis and Abderhalden. But Swingle and Uhlenhuth fed thymus extract to frog larvæ with negative results. The latter author has emphasized the fact that the delayed metamorphosis after thymus feeding may be due simply to the fact that thymus is an insufficient food.

In the whole it may be said that thymus feeding experiments have had conflicting results and have shed no definite light on the question of thymus function.

Sajous believes that the thymus being a lymphoid organ has as its function the manufacture of lymphocytes. And through these lymphocytes it supplies the excess of nucleins required in infancy to construct the nuclei of the cells of the osseous and genital systems. He believes that due to its richness in nucleins, the thymus takes part in the oxidation and autoprotective processes of the body. Also that it has some important relation to the processes of metabolism, especially with reference to phosphorus. Conclusive evidence on these points is lacking as yet.

Hoskins calls attention to the definite relationship between involution of the thymus and the decrease in the percentage of lymphocytes in the blood. He also calls attention to the relation of the size of the thymus to that of the body at different times of life. He presents a graph showing a marked parallelism between the decrease in the percentage of lymphocytes in the blood and the decrease in the relative amount of thymic parenchyma between birth and puberty.

From carefully authenticated data he has prepared a table showing the average weight of the thymus of the body as a whole at different ages, the relative amount of parenchyma and connective tissue in the thymus at different periods of life, and the percentage of lymphocytes in the blood at different periods.

His analysis of these data is given in part, below. "The table shows that although the thymus reaches its greatest absolute size at about the time of puberty, nevertheless in relation to the size of the body for all of which it functions, it is seven times as large at birth as at puberty, changing thus from 0.0385 per cent. of the body-weight at birth to 0.0055 per cent. at 14.8 years of age. The table also shows that in the growth of the thymus after birth the connective tissues make up an increasing amount of the organ. The amount of connective tissue and fat in the thymus changes from 7 per cent. of the organ at birth to 32.9 per cent. at puberty and 80 per cent. at 23 years of age. In old age the non-lymphoid part becomes nearly 100 per cent. of the thymus. Again in the absolute amount of parenchyma of this organ it nearly reaches its maximum size at nine years of age when there is present 22.08 gm. of lymphoid tissue as opposed to 25.18 gm. at puberty. This increase in the amount of lymphoid tissue is relatively much less than the relative increase of the entire body. The figures are of course averages.

"In consideration of the theory of the influence of skeletal growth by the thymus, it should be noted in the table that during the period between 14.8 and 18.2 years of age when the skeleton is growing very rapidly, the actual amount of thymic tissue decreases nearly one-half, from 25.18 gm. to 12.71 gm., and the relative amount nearly two-thirds or from 0.0055 of the body-weight to 0.0020 per cent. The skeleton also grows rapidly before puberty and while the thymus is still large. The inference here is inevitable that the thymus does not control the growth of the skeleton as is so often claimed.

* *

"A more logical theory of the significance of the thymus is that it functions as a lymphoid organ in infancy and childhood when large numbers of lymphoid cells and leukocytes are needed to combat infections. The large numbers of leukocytes and especially lymphocytes in the blood during this period of life indicates that these cells are relatively important to the organism. The question of the relative loss of thymic tissue and other lymphoid tissue all over the body that begins at birth and progresses throughout life, especially in infancy and childhood, must be bound up with the question of immunity from, or resistance to, infections that occurs in every animal. It is a fundamental law of biology that bodily structures the need for which decreases, tend themselves to atrophy."

The theory of the lymphoid nature and function of the thymus is held by many and apparently has much evidence in its favor.

In a recent thesis on the biology of the thymus Dustin says that after reviewing all the literature and the experimental work, he is forced to the conclusion that the thymus cannot be classed as an internal secretory gland, but is rather the center of nuclein metabolism acting as a reserve for nucleins which are liberated by hormones from other organs such as the liver or pancreas. So too Pappenheimer affirms that the constant (at times excessive) disintegration of nuclear

material is the most obvious form of activity taking place in the thymus. Warthin summarizes his views as to function as follows: "While we cannot at the present time absolutely deny a place to the thymus among the glands producing an internal secretion, the mass of evidence in favor of such a function is, when weighed without prejudice, very small indeed. And until the question is settled the best course to pursue seems to be to class the thymus with the lymphoid organs, inasmuch as the knowledge we do possess concerning its structure and development favors this view."

Enlargement of the Thymus.—From the standpoint of clinical interest, enlargement of the thymus occupies a place of very considerable interest. Thymic hyperplasia was the first pathologic condition of the gland to be recorded. The association of sudden death with enlargement of the thymus was noted early in the eighteenth century by Bichat, and discussion as to the pathogenesis, pathology and clinical symptoms has continued up to the present day.

In the early part of the nineteenth century, due largely to the teachings of Kopp, the theory of the etiological relationship of hypertrophy of the thymus and laryngospasm gained much credence. Indeed Kopp described typical "thymic asthma."

In 1858 appeared Friedleben's monograph on the thymus, based upon exhaustive anatomical studies. Friedleben absolutely denied the possibility of the production of laryngospasm by an hypertrophied thymus. He even went so far as to deny entirely the idea of a thymic asthma. For many years Friedleben's views were accepted as correct. But while it was everywhere admitted that laryngospasm and enlarged thymus had nothing to do with each other, anatomical studies on the thymus were published by such authorities as Cohnheim and Virchow. These were supplemented by clinical studies by a host of careful observers. The published records showed not only that dyspnea from enlarged thymus is a possibility but that true thymic asthma does actually occur. The discussion of the association of enlarged thymus with sudden death became exceedingly active. To explain these cases of so-called thymic death, various theories, based on clinical, anatomical or experimental studies, were advanced. The possibility of such thymic death by direct pressure on the trachea with resulting asphyxia, by compression of the large vessels at the base of the heart, or of pressure on mediastinal nerves, by a flooding of the system with an excess of thymic secretion (Svehla's hyperthymization) was emphatically proclaimed. And the claims were apparently substantiated by the anatomical findings. On the other hand, these theories were as vigorously denied by observers whose reasoning and evidence did not lack force.

New light was thrown on this vexed question of thymic death by the masterly monograph of Paltauf published in 1889. As the result of his anatomical studies Paltauf came to the conclusion that enlargement of the thymus constituted but one manifestation of an abnormal constitutional state. He found that in his cases of sudden

death with apparent cause, there was not only an enlarged thymus, but in addition a marked hyperplasia of the lymphoid apparatus of the body, of the faucial tonsils, of the intestinal follicles, together with enlargement of the spleen and hypertrophy of its follicles. In addition to these changes in the lymphoid system, there was a characteristic picture in the circulatory system. The aorta and the smaller arteries were thinner walled and smaller than normal, so that there was real hypoplasia of the entire arterial system. In some of the cases there were signs of acute cardiac dilatation, sometimes there was more or less myocardial degeneration. In older patients showing the signs of this condition Paltauf was able to show the blood picture of chlorosis, and so his name of lymphatic chlorotic constitution finds its justification. More commonly the condition is known simply as status lymphaticus.

In the light of recent studies and experience it appears certain that enlarged thymus may exist without the association of the other constitutional anomalies of the status lymphaticus. It is doubtless true that at times the enlarged thymus produces no symptoms whatever. In some of these cases as the result of trivial trauma, slight infection or anesthesia, sudden death occurs. It is probable that some cases of so-called "overlaying" belong in the category of thymic death. But in most cases some symptoms are noted before death and it is certainly true that careful *routine* examination would disclose the signs of enlarged thymus wherever the anomaly exists.

For convenience of discussion enlargement of the thymus will be treated as a separate clinical entity, reserving a consideration of status lymphaticus for later review.

Occurrence.—According to some clinicians enlargement of the thymus is supposed to be rather a rare condition. Those of us who have been particularly interested in the question have been able to prove the fallacy of this view. The condition is in reality quite common. It is rather astounding to note how frequently it is to be found if it be systematically searched for. Thus Benjamin in his individual service in the children's out-patient clinic (University of Cincinnati—College of Medicine) had 225 new cases all told, in a year's time. Of these 19 showed indisputable evidence of enlarged thymus (8.4 per cent.). No other physician in the out-patient department found so many cases, because no other physician examined his cases so carefully with reference to this particular condition.

Etiology.—In a few cases thymic enlargement may be due to congestion resulting from acute infections or circulatory disturbances. But in the majority of cases we are dealing with a true hyperplasia. As Warthin puts it: "For this condition it is very probable that there is a varied etiology. The primary cause may be sought in any infection, intoxication or disturbance of metabolism in which there is a lymphoid or a myeloid exhaustion. The enlargement of the thymus is, therefore, a secondary process of the nature of a compensation."

The association of enlarged thymus with congenital syphilis and with rickets has been noted by various observers. Warthin regards

this as compensatory for the splenic fibrosis which occurs in these cases.

Pathology.—The underlying pathologic picture is hyperplasia of the lymphoid tissue of the thymus. And it is just the lymphoid tissue which preponderates in early life when hypertrophy of the thymus, is most common. It will be recalled that Hoskins has pointed out that the thymus is heavier in relation to body weight at birth than it is at puberty, though relatively it is larger at puberty.

While there is no definite agreement as yet as to the actual weights of the thymus at birth, it seems safe to say that thymi weighing more than 15 gm. are hyperplastic. Weights up to 150 gm. have been reported, and as Warthin points out, the post-mortem size and weight of the thymus may afford no real index of its size and weight before death.

My observation has shown that an increase in the thickness of the thymus anteroposteriorly is of much greater importance than increase in size in other directions.

At the superior opening of the thorax of a young child, the so-called critical space of Grawitz, the anteroposterior diameter measures only 2 cm. from sternum to vertebral column. In this space are contained, between unyielding walls, trachea, esophagus, great vessels and nerves, and the thymus. It is obvious that a greatly *thickened* hypertrophied thymus would cause compression of the structures behind it, and as a matter of fact tracheostenosis, as a result of enlargement of the thymus has repeatedly been demonstrated. Scheele's argument against the mechanical compression theory, namely, that it takes a weight of 750 to 1000 gm. to flatten the trachea of a child post-mortem, lacks cogency. We have no way of determining the intra-thoracic pressure produced *intra vitam* by an enlarged thymus. It is a question of diminution of the narrow mediastinal space, and not one of mere weight of the gland. Again, with the tracheoscope it has been possible to *see* the flattened trachea in many instances. Warthin calls attention to the fact that the trachea of a child is very elastic, that it tends to resume its normal shape as soon as any pressure on it is relieved. He advises, therefore, that the neck organs be examined *before* the thymus is removed in order to demonstrate tracheal stenosis at autopsy. He also points out that compression of the trachea by the enlarged thymus may be demonstrated by fixing neck and thorax of the child in formalin and alcohol before these organs are sectioned.

No other theory explains the signs and symptoms of enlarged thymus as well as the one of mechanical compression. As has been pointed out heretofore, absolute evidence of a thymic secretion is lacking and Svehla's theory of hyperthymization (intoxication of the organism with excess of secretion) lacks any confirmation whatever.

It may well be that all of the signs and symptoms may not be due to tracheostenosis, but it will be remembered that the great vessels and the great nerves are also compressed in the critical space of Grawitz, and such compression may be a real factor.

Symptoms.—There are three cardinal symptoms of enlarged thymus, which may be present in varying degrees of severity and in different combinations. These symptoms are, dyspnea either continuous or remittent, suffocative attacks, and stridor.

The symptom must commonly present is dyspnea, either continuous or remittent. Olivier in his monograph on the surgery of the thymus used this symptom as a means of classification of cases. The continuous form of dyspnea is the type most often seen in very young infants. The respiratory difficulty increases until the child has a suffocative attack accompanied by intense cyanosis. These suffocative attacks may come on suddenly without warning or follow fits of screaming or crying, particularly if the head be thrown back. These attacks are repeated with greater or less frequency and death may occur during one of them. Between the attacks the dyspnea is continuous.

In the intermittent forms, children apparently quite normal, and usually several months of age, are suddenly seized with suffocative attacks accompanied by intense cyanosis, usually with convulsive movements of the extremities, followed after a few moments by a return to an apparently normal state. The intervals between the attacks, at first considerable, tend to become constantly shorter. Variations and gradations of the two forms are common, and have been frequently described.

The second symptom of frequent occurrence is stridor.

This is usually inspiratory, though in extreme dyspnea an expiratory stridor is sometimes heard. In some cases the stridor is present from birth, some time before even the dyspnea.

Now there can be no question of the very frequent association of congenital stridor and enlarged thymus. But it is surely not correct to assume, as do Haerttel and Hochsinger, for instance, that congenital stridor is always due to enlarged thymus.

Refslund and Koplik have shown that in certain cases of congenital stridor there is a peculiar malformation of the superior opening of the larynx. "The epiglottis has a gutter or beak-like form and is folded in the middle line" (Crotti).

Again, Lees and Thomson have shown that occasionally congenital stridor is due solely to incoördination of the vocal cords, the result of muscular imbalance. The diagnosis of enlarged thymus is thus certainly not justified on the finding of congenital stridor alone, though the presence of this symptom should in every case awaken suspicion, and lead to careful physical examination.

This should include, as a matter of routine, the search for evidence of pathologic change in the naso-pharyngeal lymphoid ring, and particularly of the follicles at the base of the tongue. There has been much discussion as to the possibility of actually diagnosticating the presence of the enlarged thymus itself, but with the means at our command today, there can be no question of our power to do so.

Physical Signs.—The physical signs of enlarged thymus are these: Detection of a mass in the jugulum by palpation, enlargement of the

area of thymus dulness on percussion, the demonstration of tracheostenosis by bronchoscopic examination, or intubation, a special blood picture, and finally, the special type of thymus shadow as demonstrated by the *x*-ray.

In some cases palpation in the jugulum reveals the presence of a soft tumor, to be felt best during expiration. Attention was first called to this point by Rehn, but it must be admitted that it is an uncertain sign at best. This holds good also with reference to the bulging of the manubrium, a sign surely absent in the majority of cases of enlarged thymus.

Percussion yields definite information of great value. Sahli and Blumenreich have formulated the principles for outlining the thymus by percussion. Blumenreich came to the following conclusions as the result of his studies: In young children there is a definite form of thymus dulness in the shape of an irregular triangle or truncated cone, whose base is the sternoclavicular junction and whose apex is the second rib. The sides extend but very slightly beyond the margins of the sternum, slightly more on the left than on the right side. Dulness extending more than 1 cm. on either side, concealing the note of pulmonary resonance between the heart dulness and the normal area of thymus dulness, shows, in the absence of other causes, an enlarged thymus.

Simply engorged lymph-nodes in the anterior mediastinum cause no dulness, while caseous nodes do. An important point to be noted is that dulness directly continuous from thymus to heart is always significant. Boggs has claimed that the thymus dulness is movable, depending on whether the neck is flexed or extended, the difference amounting almost to an interspace. Personally, I have not been able to convince myself of this movable dulness, and Park and Maguire have shown the incorrectness of Boggs' views, as the result of their anatomical studies. It may be remembered that Jacobi has claimed that the thymus is movable in the anteroposterior direction and that he has suggested percussing the thymus site with the child on its back and then percussing the area again from underneath with the child held face downward. So far as I know, there has been no confirmation of his findings of thymus motility in the anteroposterior direction.

Basch and Rohn have devised a special instrument for the percussion of the thymus. They claim that by its use in combination with auscultatory percussion and friction it is possible to obtain a more exact estimate of the size and condition of the thymus than has hitherto been the rule. The instrument offers no advantages over careful threshold percussion.

The bronchoscope has enabled skilled observers to demonstrate the existence of a tracheostenosis in certain cases of enlarged thymus. This diagnostic method (first employed by Jackson) is, however, of limited application only, owing to the difficulty of laryngoscopic and bronchoscopic examination in young children. Intubation has occasionally led to the diagnosis of enlarged thymus, as in Rehn's first operative

case, where the long tube had demonstrated the presence of obstruction low down in the trachea. In cases of enlarged thymus in association with status lymphaticus, the blood picture may be of diagnostic value. Thus in a case reported by Rachford in a child one and one-half years old, the differential blood count showed a total lymphocytosis of 72.8 per cent. with the general blood picture of chloranemia. Naturally, in older children a marked lymphocytosis is of greater diagnostic import than in young infants.

The diagnosis of enlarged thymus has, however, been simplified very greatly of late by the means of the *x*-ray. At the outset it should be noted that for this diagnostic work, especially in young infants, high-power machines, taking almost instantaneous pictures, are essential. With the slower machines the shadows are often so blurred, owing to movements of the child, as to greatly diminish their diagnostic significance. Great emphasis is laid on this point by Lange of Cincinnati, who has had a very considerable experience in thymus radiography. Since the appearance of Hochsinger's monograph, the use of the *x*-ray as a diagnostic method in enlarged thymus has become universal.

The *x*-ray shadow of enlarged thymus is a wide median one. In some cases the broad shadow continues up directly from the heart shadow, in others the thymus shadow appears like a broad cap superimposed on the shadow of the heart and vessels. It must be admitted that a broadening of the shadow above the heart is not always due to enlarged thymus. In a careful study of the interpretation of the thorax radiogram in the nursling, Benjamin and Goett point out that a broadening of the shadow to the right may at times be due to the large vessels, especially the vena cava superior. But, as they note, this cannot hold good when the larger part of the shadow falls to the left of the vertebral column.

Ferrand and Chatelin find that the thymus and heart give a distinct sharp median shadow. Enlarged bronchial glands give an extra median shadow, separate from the heart shadow and not connecting with it. This latter point is of importance. Myer has also called attention to it. There does not appear to be any question as to the diagnostic value of the *x*-ray in many cases of enlarged thymus. But even as experienced a radiographer as Lange expressly insists that in certain cases, especially if the gland be increased in size laterally without augmentation of its anteroposterior diameter (the large flat thymus), the *x*-ray picture may not be conclusive. As has been well said: "Where the *x*-ray evidence is positive, it is of real value in diagnosis, but when it is negative it is not to be considered as final."

The *x*-ray gives *no* indication of the thickness of the gland and, on the other hand, a very thick gland may give rise to symptoms of compression without showing a greatly increased radiographic shadow. But after all is said the *x*-ray remains the most valuable diagnostic agent we have in the diagnosis of enlarged thymus. It must be emphasized, that in order to get satisfactory radiograms, without blurring, the exposures must be exceedingly short, preferably not exceeding

one-thirtieth of a second. With modern high-power tubes, such short exposures suffice to give excellent pictures and the danger of blurring on account of movement of the patient is reduced to the minimum.

Prognosis.—Until the advent of *x*-ray therapy, the outlook for patients with enlarged thymus was distinctly grave. Palliative measures were of very little avail and the operation of thymectomy was attended by a high mortality. Children with enlarged thymi were in constant danger of sudden death as the result of trivial intercurrent infections such as coryza or mild bronchitis, or as the result of mere emotional excitement. They bore anesthetics exceedingly badly, indeed many "anesthetic" deaths in infancy and childhood, or even in later life, are in reality thymic deaths.

But with the *x*-ray this has all been changed. The mortality has been tremendously reduced, and the prognosis in cases recognized early enough and properly treated is exceedingly good.

It should be made the rule to suspect enlarged thymus whenever *any* of the signs and symptoms are present. Verification of a diagnosis on suspicion can be had very promptly by means of the *x*-ray. With a positive diagnosis, *x*-ray treatment may be begun at once, with assurance of success in most cases.

Treatment.—Reviewing the recent literature, summing up the clinical and experimental evidence, it must be admitted that the enlarged thymus causes its effects very largely as the result of the direct mechanical pressure it exerts. It is the physically enlarged thymus which gives rise to the threatening symptoms and is the source of danger to the child. Drug treatment is of absolutely no avail, indeed it has long been recognized that drugs had no power to relieve thymic asthma, and recourse was, therefore, had to:

Surgical Treatment.—The first operation was done by Rehn in 1896. He did an exothymopexy. This operation consisted in lifting the thymus from its place behind the sternum and fastening it to the tissues of the neck or the top of the sternum. The results of this operation were not good and it was soon superseded by the operation of thymectomy. The technique of this operation was worked out by French surgeons, especially Veau and Olivier. The latter published an exhaustive monograph in the topographic anatomy and surgery of the thymus. A collection of all reported operative cases, together with a resumé of the entire question, was published by Parker in 1913. Of the 50 patients operated upon, 17 died, showing a mortality of 33 per cent. Even excluding some of the fatal cases, as Parker does for good reason, the fact remains that the mortality of the operation is high. And it cannot be considered as definitely proved that the complete removal of the thymus in infants, at a period of supposed functional activity, is not fraught with some danger to the later development of the individual. As a matter of fact the operation is done very rarely nowadays, partly because of its danger and partly because it has been superseded by a safer and far more effective method of treatment. This is the:

X-ray Treatment.—In 1903 Heinecke published his studies on the effects of the *x*-ray in lymphoid tissues. He exposed young animals to the *x*-ray on successive days, then killed the animals and later studied the changes in the lymphoid structures. He found that the spleens of the animals showed marked changes: Increase of pigment, disintegration of cells, reduction in size of the Malpighian follicles and rarefaction of the cellular elements. He suggested that it might be possible that in the human being analogous changes might occur without skin reaction. In 1904, I had under observation a typical case of status lymphaticus with a greatly enlarged thymus in a two months old infant. The suffocative attacks were very severe, with constant dyspnea and cyanosis.

In view of the desperate character of the case the parents consented to allow the use of the *x*-ray though of course no definite promise of relief could be held out. Twelve exposures in all were given, over a period of one month. The improvement was rapid, the suffocative attacks ceased, the thymus dulness came down to normal limits. The subsequent development of the child was absolutely normal, and at this writing the boy is well and strong, indeed decidedly athletic.

This was the first case of enlarged thymus successfully treated by the *x*-ray. Its publication was purposely delayed until 1907 in order that there could be no question of the result.

Since this time experimental studies by a number of investigators have demonstrated that it is possible to induce involution of the thymus by the *x*-ray. Aubertin and Bordet, Rudberg, D'Oelsnitz and Paschetta, and Regaud and Cremieu among others have studied the process of such artificial involution in detail.

In order to formulate the technique of *x*-ray treatment in cases of enlarged thymus, Lange and I conducted a series of experiments on rabbits under proper control and showed that it was possible to reduce any degree of fibrosis of the thymus, from the very slightest to absolutely complete fibrosis. Our experimental work showed that it is possible to bring about involution of the thymus with varying degrees of rapidity, by variation in the number and time intervals of *x*-ray exposure. The clinical importance of this is that involution can be hastened if necessary where cases are urgent, by exposures on successive days. We found that it was possible in our animals to induce any degree of fibrosis desired, so that clinically the dosage of *x*-ray can be regulated according to the necessities of the case.

Though we were particularly careful to allow only the thymus region of the animals to be exposed to the rays, we found that the spleens of the animals showed reduction in number, size and clearness of the outline of the Malpighian corpuscles, correlated in degree to the amount of fibrosis in the corresponding thymus. Clinically we found that in cases of enlarged thymus associated with status lymphaticus, treatment of the thymus region alone was followed by reduction in size of the spleen and lymph-nodes, while the blood picture changed from a lymphocytic to a normal one.

Experimentally we found also that a thymus partially involuted by the *x*-ray is capable of regeneration. So that there can be no danger of loss of thymus function, whatever that may be, as the result of *x*-ray treatment.

In the nine years that have elapsed since the publication of this experimental work, the treatment by *x*-ray has become the treatment of choice with the majority of men handling such cases. Our own records in the Cincinnati General Hospital show a series of over 250 cases, with two deaths.

Fig. 138.—Baby L. 6 days old.

X-ray Technique.—The technique of the *x*-ray treatment as worked out by Lange is as follows: A Coolidge tube backing up a 9½ in. spark is employed. The rays are filtered through 4 mm. of aluminum and a piece of thick leather. The target skin distance is approximately 9 in. For children over three months of age, the routine exposure is 25 milliampereminutes; for children under three months of age 15 milliampereminutes. In mild cases a single dose given over the anterior surface of the chest often proves sufficient. In more urgent cases, 50 milliampereminutes are administered, 25

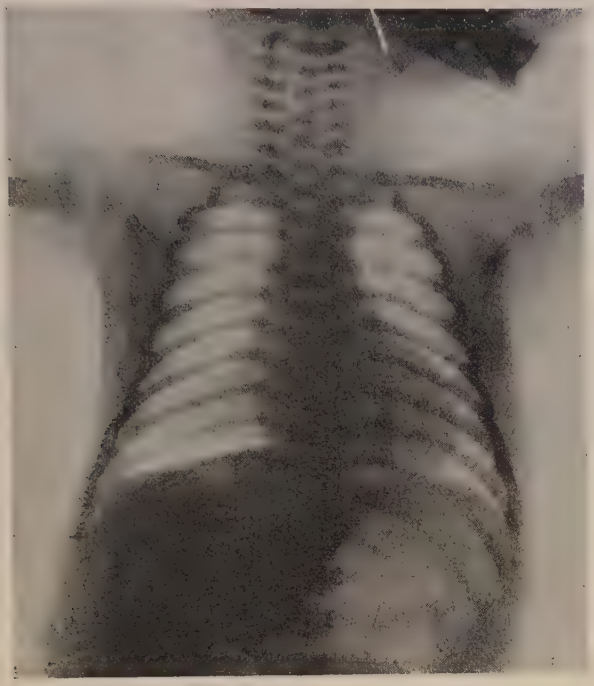

FIG. 139.—Baby L. 13 days old.

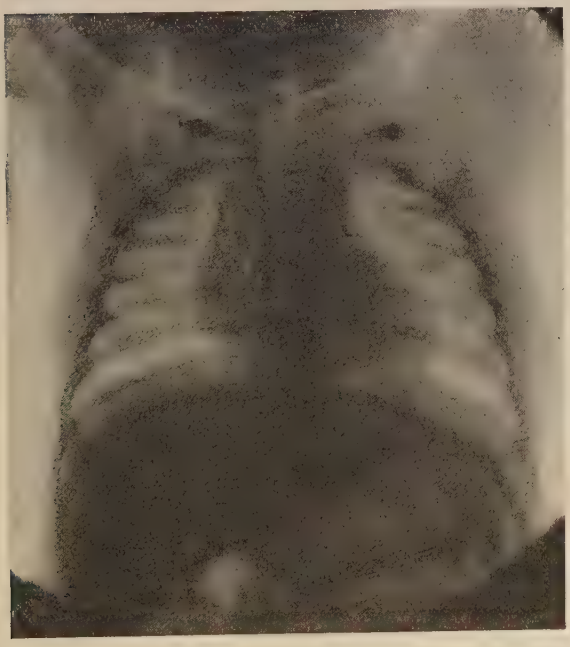

FIG. 140.—Baby G. 10 weeks old. 10–24–16.

anteriorly and 25 posteriorly. During the treatment the child is kept quiet by four sandbags, one placed across each arm and one placed across each leg.

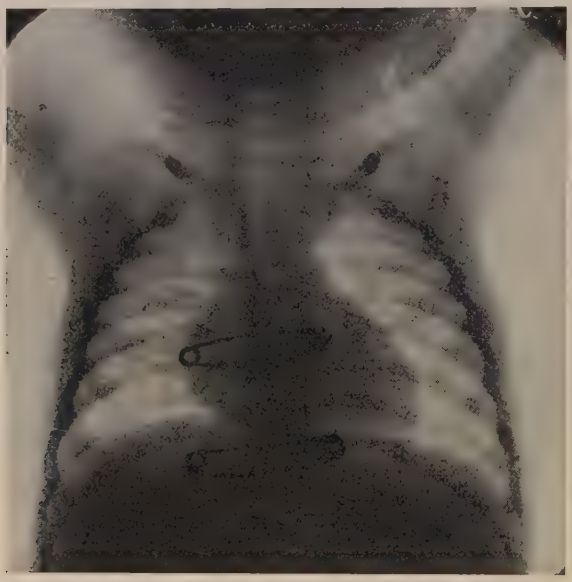

FIG. 141.—Baby G. 12 weeks old. 11–7–16.

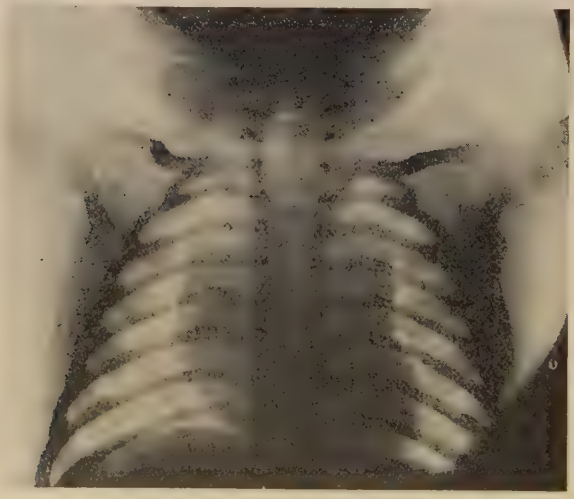

FIG. 142.—Baby F. 10 weeks old. 8–20–18.

The intervals between treatments have usually been one week, unless the urgency of symptoms has suggested more frequent applications. If the symptoms are very urgent, daily treatments may be given for two or three days. In very severe cases with very frequent

suffocative attacks, intense cyanosis and persistent stridor, it is essential that the treatments be comparatively heavy and that they be repeated at sufficiently short intervals.

The failure to administer full doses and to repeat them promptly has in very severe cases led to fatalities under *x*-ray treatment. Such a distressing occurrence is, fortunately, uncommon, but when it does happen it casts a doubt on the diagnosis or on the efficiency of the *x*-ray treatment. To guard against sudden deaths before the full destructive effect of the *x*-ray on the thymus has been elicited, all

FIG. 143.—Baby F. 3 months old. 9–5–18.

patients with urgent symptoms should be kept under close observation, and the *x*-ray treatments should be pushed boldly.

In the average case, improvement of symptoms has been noted within 24 or 48 hours after the first treatment. It is possible, however, as shown by animal experiment, to produce changes in the thymus within eight hours after exposure. Therefore, even the most urgent cases may be expected to yield to the treatment if the dosage be sufficient.

Figures 138–143 are taken from our series at the Cincinnati General Hospital, and my thanks are due to Dr. K. F. Little for them. They are shown in pairs for each case. First before treatment: Second after treatment, with dates. Clinical experience of many observers in many places has now determined not only that

x-ray treatment is the treatment of choice in these cases, but that it is effectual, sure and safe. No bad after effects follow its use in competent hands, and the treatment is one which has rendered an almost hopeless condition, and a rather frequent one, easily curable. In the judgment of many clinicians it should be used in all suspicious cases even though the diagnosis be not positive. Thus Cook says that children physically or mentally retarded should receive treatment on the chance that a hyperplastic thymus may be an element. He holds that precautionary *x*-ray treatments should be given to children of lymphatic type to enable them to withstand better any intercurrent infections or any possible necessary anesthesia.

Radium Treatment.—Recently several observers have reported excellent results with radium, as a substitution for the *x*-ray. One obvious advantage in favor of radium is that it eliminates the element of fright in the infant or young child. This may be a matter of importance, for the fixation necessary in *x*-ray work may induce an attack of thymic asthma. Heublein has recently reported a series of cases of enlarged thymus successfully treated by radium. The technique followed was "Cross firing with 100 mg. of radium element, filtered through 0.3 mm. silver at a ½ in. skin tube distance through four portals of entry, the tube being placed over the anterior aspect of the chest directly over the thymus gland. The tube is left two hours in each position, which makes a total dosage of 800 mg.-hr." In his later work, recognizing that time is such an important factor in these cases, the author has substituted 200 mg. with half the time of exposure. Heublein states that one treatment is all that is required, that there is no danger of over-treatment, that further advantages of radium consist in its portability, its ease of administration and its safety, in that the skin tube distance never varies in the most refractory child.

Status Lymphaticus.—Status lymphaticus is a constitutional anomaly whose outstanding features are hyperplasia of the thymus, hyperplasia of the lymphoid tissues in various parts of the body, including tonsils, pharyngeal lymphoid ring, lymph-nodes, lymphoid tissue of the intestinal follicles. With this there is enlargement of the spleen. Also there is a marked hypoplasia of the cardio-vascular system and developmental deficiencies in the genitalia. The condition is often terminated by sudden death. It was originally described by Paltauf in 1889, who called attention to the medico-legal aspects of the sudden death in these cases.

The condition is compatible with life, as proved by the fact that many of its victims live to maturity. But the condition is dangerous because of the liability of its victims to fatal anaphylactic shock from sensitization through an impaired lymphoid apparatus, because of the lowering of resistance to infection and because of the cardio-vascular defect.

Clinically two types may be recognized. One, the delicate fine featured child with particularly clear skin, transparent scleræ, well but under-proportioned. In the other the skin is coarse and pasty

looking, there is a tendency to recurring eczema with the picture of rickets.

At puberty in both groups there is a lack of development of the genitalia. The over-development of the lymphoid tissue persists, faucial tonsils, pharyngeal ring, enlarged lymph-nodes being especially prominent. In association with these abnormalities the thymus is hyperplastic (or "persistent" in older individuals) in all cases and the dangers resulting from enlarged thymus are ever present. It is this fact which gives added importance to the recognition of the condition. It had been supposed that status lymphaticus was of somewhat infrequent occurrence, but recent studies have shown the falsity of this view. In 1918 Symmers published a statistical study which showed that in Bellevue Hospital 457 cases of status lymphaticus were encountered in 5652 autopsies (8 per cent.). Some of the outstanding features of Symmer's analyses of the first 249 cases follow:

The condition was found much more frequently in males than in females, in the proportion of 6:1.

Two types of the condition are described, status lymphaticus and recessive status. The former shows over-development of the lymphoid tissues and occurs at an age when the lymphoid tissue is functionally most active. The recessive type is marked by atrophic changes in the lymphoid tissues.

Of the 118 cases of true status lymphaticus, the thymus was hyperplastic in every instance. In the recessive cases this was not true, and in 70 of the 89 recessive cases the thymus was not visible to the naked eye. While the lymphoid follicles of the spleen were enlarged in 88 per cent. of the true cases, the spleen itself was enlarged in only 30 per cent., and in these, special etiologic factors to produce splenic enlargement were found. Symmers holds that enlargement of the spleen is not a true part of the pathology of status lymphaticus.

Histologically the thymus showed typical hyperplasia of the cortical lymphoid follicles. In some cases these were large blood sinuses in the thymus containing greatly increased numbers of lymphocytes. The lymph-nodes also showed greatly increased numbers of lymphocytes. In addition, in many instances, the lymph-nodes showed a peculiar necrosis of the germinal areas which have been described by other writers also. Symmers believes this peculiar histologic change to be pathognomonic of status lymphaticus and of fundamental importance in the interpretation of anaphylaxis as the cause of sudden death and of the convulsive phenomena that occur in status lymphaticus.

Cardiovascular System.—In 51 per cent. of the 249 cases the heart was small or normal in size. In 40.5 per cent. of these same cases the aorta was hypoplastic.

Seven cases of hypoplasia of the cerebral arteries, with rupture, were found in the series.

Finally, it is of special interest to note that of the 249 cases, 222 (88 per cent.) showed some form of acute infective lesion. Of these the commonest were endocarditis, pneumonia and meningitis.

Atrophy of the Thymus.—Aside from the normal involution of the gland it is well known that retrograde changes in the thymus of all degrees occurs as the result of various infections and as a concomitant of certain other diseases. Thus it has long been known that in marasmus and rickets the thymus shows very definite recessive changes. For a time it was even believed that there was a causal relationship between the thymic degeneration and marasmus and rickets. This view is not held at the present time. The thymic change is the result of rather than the cause of the diseases.

Takeuchi has made a careful study of the changes in the thymus in various infectious diseases, including "Ekiri," enteritis, dysentery, pneumonia, diphtheria, septicemia and tuberculosis. He collected 262 cases of which 162 were specially carefully examined. He found the chief changes to be degenerative and destructive. There was destruction of the small thymus cells of cortex and medulla, degenerative enlargement of Hassall's corpuscles and enlargement and phagocytosis of the cortical reticulum. It was possible to recognize a primary increase and secondary atrophy of the parenchyma, an initial increase and subsequent decrease of the eosinophile cells followed by an increase of connective tissue.

In most acute infections there is a tendency to destruction, while in the more chronic diseases there is more tendency to atrophy. On the other hand, the studies of Vasyutochin led him to somewhat different conclusions. He found that in gastro-intestinal diseases there was apt to be a thymic hyperplasia. Diseases of the respiratory tract, non-tuberculous, produce no marked changes other than those due to malnutrition. There was also no effect on the thymus in septic cases. In tuberculosis and diphtheria there was some diminution in the size of the thymus. Congenital syphilis produced marked atrophy of the thymus.

Oliver has made a study of syphilitic disease of the thymus in infants. He reports a case showing the "abscess cavities" of the thymus originally described by Dubois in 1850. These cavities are characterized by a lining of stratified squamous epithelium and contain material that looks like pus. In Oliver's case there did not appear to be any question of the formation of the abscesses by cyst-like dilatation and coalescence of the Hassall bodies. In addition to the Dubois abscesses the syphilitic thymus is characterized by preponderance of reticulum and disappearance of the lymphocytes from the gland. Warthin believes that the so-called Dubois abscesses are at times simply broken down gummata. He adds that he finds spirochetes in great numbers in the thymus without recognizable histologic changes in the great majority of cases of congenital syphilis. Certain it is that the so-called Dubois abscesses are *not* characteristic of syphilis, as they are found very commonly in thymus involuting normally, or as the result of any one of many infections.

The Thymus in Exophthalmic Goiter.—The association of hyperplasia of the thymus and exophthalmic goiter has been noted by

many observers. Mackenzie, who made a careful study of Graves' disease including mortality statistics for England and Wales, says that in 36 post-mortem examinations held on cases of exophthalmic goiter at St. Thomas' Hospital, the most constant feature next to the thyroid enlargement was the presence of a hyperplastic thymus. Similar findings have been reported by many other observers. The exact relationship of the two glands in the production of the syndrome of Graves' disease is still the subject of much discussion.

Klose says that the thymus undergoes morphologic change in Graves' disease (epithelization) and that it can "thymusize" the thyroid. The two glands can cause a general hyperplasia of the lymphoid system.

Eddy attempted to determine whether an excess of the product of thymic activity in the circulatory blood could cause Graves' disease. He injected large doses of thymus gland substances into rabbits over a period of eight weeks. Forty injections were given to each rabbit. No symptoms of Graves' disease were produced. A review of the literature, however, he adds, seems to indicate the existence of some relationship between the thymus and Graves' disease, the exact nature of which is not clear at the present time.

It is held by many that the influence of the thymus is responsible for certain phases of the syndrome of Graves, e.g., dyspnea and lymphocytosis. Halsted believes that the association of the thymus should be thought of in cases of Graves' presenting marked dyspnea, diarrhea and slight enlargement of the thyroid without exophthalmos or tachycardia.

Clinically the presence of thymic hyperplasia in Graves' disease is of very definite import. Under no circumstances should operation for Graves' be undertaken, even under local anesthesia, without previous *x*-ray examination to exclude the presence of an hyperplastic thymus. Nordmann even advocates thymectomy, where there is an enlarged thymus in Graves' disease, before doing a thyroidectomy. Certainly such an antiquated view can find little support. But the value of inducing involution of the thymus by the *x*-ray before operation is of course not open to question. The excellent results of *x*-ray treatment in Graves' disease in many cases, the apparent frequency of hyperplasia of the thymus in this condition, and the probable association of the two glands in the production of the disease are well known. It becomes a matter of interest to speculate as to whether the improvement that follows the use of the *x*-ray may not in some measure be due to the shrinkage of the thymus.

Tumors of the Thymus.—It is now generally believed that tumors of the thymus are more common than was formerly believed. It must be remembered that at least some of the tumors said to be thymic tumors are in reality primary in the mediastinal lymph glands. As proof that a tumor is primary in the thymus, it is generally held that Hassall's corpuscles must be demonstrable. Strauss holds that the diagnosis of thymic tumor is justifiable even in the absence

of Hassall's corpuscles, and Litulle has taken the view that retrosternal tumors high up, where there is no involvement of the mediastinal glands, probably arise from the thymus.

True thymic tumors are as a rule either lymphosarcomata or carcinomata, the former occurring more often in young life, the latter in later life. In the leukemias it is well known that there may be secondary localizations in the thymus, as we see them in other lymphoid structures of the body. And as Warthin points out, in the late stages of Hodgkin's, the thymus usually shows changes similar to those found in the lymph-nodes, while in the earlier stages such changes are not present.

Reviewing this subject of thymic tumors Ewing points out that the lymphosarcomata of the thymus probably spring from the reticulum cells of the gland. Spindle-celled, or myoxosarcomata, are very rare.

Discussing the question of malignant tumors of the thymus, Janeway notes that the early symptoms are cough, without expectoration or hemoptysis and marked dyspnea. The picture is somewhat like that of pulmonary tuberculosis, and the diagnosis is often facilitated by the *x*-ray. He believes that radium applied early is of real value, in that it usually affords relief and in certain cases even prospect of cure.

Special interest attaches to the thymic tumor that is found in some cases of:

Myasthenia Gravis.—Starr found a pathologic condition of the thymus in 28 of the cases that came to autopsy. In another series of 56 cases, collected by Bell, the thymus was enlarged in 17 cases, and in 10 others contained a tumor. The thymic tumors as seen in myasthenia according to some authors form a distinct group unlike any other thymic tumors, and are classified as benign thymomata. Bell finds that some abnormality of the thymus is found in nearly half of the cases of myasthenia. Such an association has been reported by others, also, but no definite theory of causal relationship has been established. Indeed it is well known that several of the ductless glands show change in myasthenia.

The Thymus and Certain Abnormal States.—Enlargement of the thymus has been observed in certain forms of dwarfism, in achondroplasia, in severe cases of acromegaly, in Addison's disease and in myxedema. So far we are unable to say whether these associations are very frequent, or whether they stand in any sort of causal relationship to these various abnormal conditions.

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CHAPTER LXXXII

DISEASES OF THE THYROID GLAND

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Historical.—Although goiter and cretinism have been known for many centuries, Gull, in 1873, recorded the first clinical description of myxedema, regarding the same as "a cretinoid state." Ord, in 1875, gave the name of "myxedema" to such cases, Charcot, in 1879, supplying the term "cachexie pachydermique," with a clinical description. Kocher and Reverdin discovered the connection of myxedema with thyroid deficiency. Pineles contributed his important studies on athyrosis at the end of the nineteenth century. The influence of thyroid disease on basal metabolism was first studied by Magnus-Levy. Important metabolic studies have been recently made in American medical centers by Du Bois, Means and Aub, Plummer, etc. E. C. Kendall, in 1917, announced the preparation of the isolated thyroid hormone which he later synthetized and supplied the structural chemical formula. This represents the most important advance of the twentieth century in regard to knowledge of the thyroid. Marine and Lenhart, also McCarrison in India, have lately contributed important studies on the experimental production of goiter.

Embryology and Topographical Anatomy of the Thyroid Gland.—The thyroid develops as a median evagination of the ventral wall of the fore-gut. Thus the gland is primarily one of external secretion, but its *thyroglossal duct* usually becomes obliterated, though it may rarely remain as a fetal rest connected with the root of the tongue. The post-branchial bodies, probably rudimentary fifth branchial pouches found attached to the fourth pair of these organs, may develop thyroid tissue. It remains uncertain, however, to what extent this occurs under normal conditions. The solid evagination produces epithelial cords which become interwoven with connective tissue. The cords develop by partition into solid spheres which later become hollow follicles lined with secretory epithelium. By the fourth fetal month, the gland has already nearly reached its normal appearance. The follicles may already contain colloid after birth, but thereafter exhibit masses of cells which have been cast off by the lining epithelium. Later these cell accumulations reattach themselves to the follicle walls. According to certain observers, however, this desquamation of cells is a post-mortem phenomenon.

The weight of the thyroid gland varies according to geographical location. Thus this organ is generally heavier in mountainous regions, particularly those in which goiter is endemic. According to Hessel-

berg, the weight of the thyroid about the age of birth varied in Berne, Switzerland, from 4.1 to 6.6. gm., but on the plains, was only 1.56 gm. According to several authors, the weight of the gland in comparison to the body-weight bears the relation of 1:400–243 in the newborn, 1:1166 in three weeks old children, and 1:1800 in adults.

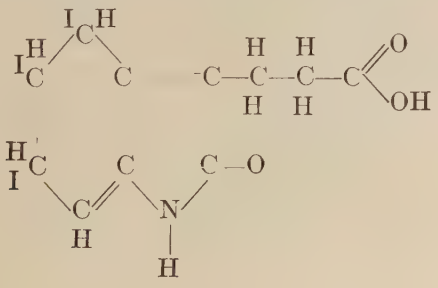
The thyroid gland lies in close connection with the trachea and larynx, rising and falling with deglutition. The two large, conical, lateral lobes are directed upward and outward as far as the junction of the middle with the lower third of the thyroid cartilage. The lateral lobes are united by the isthmus covering usually the second and third tracheal rings. A third pyramidal lobe may occasionally be present, arising from the isthmus. The convex external surface of the gland is covered by the skin, superficial and deep fascia, the sternomastoid, sternohyoid and sternothyroid muscles. Beneath these muscles lies the outer fascial capsule of the gland. From this inner capsule, lamellæ of fibrous tissue penetrate between the lobules of the gland. Small detached rests of thyroid tissue may be found above the isthmus or, indeed, anywhere from the base of the tongue downwards to the heart.

The thyroid is unusually vascular, being supplied by the large-sized, paired, superior and inferior thyroid arteries, and occasionally, in addition, by the *thyroidea media* arising directly from the innominate or aorta. The superior middle and inferior thyroid veins empty into the external jugular. The lymphatics are large-sized and numerous. Histologically, the gland consists of innumerable closed vesicles containing more or less colloid material and lined with a single layer of cuboidal epithelium. Between the vesicles are the connective tissue stroma, lymph spaces and a rich vascular network.

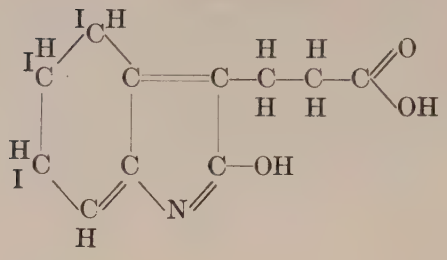
Chemistry and Function of the Thyroid Gland.—In view of the brilliant researches of E. C. Kendall, 1910 to 1920, resulting in the isolation and establishment of the structural formulæ, chemical characteristics and physiologic action of the thyroid hormone, it seems superfluous to review the various chemical studies antedating this work. According to Kendall[1] the thyroid hormone designated by him as thyroxin, a colorless crystalline substance, is 4, 5, 6, trihydro -4, 5, 6 tri-iodo, -2 oxy, -beta indoleproprionic acid, containing 65 per cent. iodin and having the following structural formulæ;

Schema I.—Structural Formulæ of The Thyroid Hormone (Kendall)

Keto Form



Enol Form



There is (2) a tautomeric enol form, also (3) an open ring form, and (4) a tautomeric modification of the third form. Experimentally thyrotoxic symptoms and great increase of the basal metabolism were found to follow administration of the isolated hormone. Thyroxin in excess causes a large increase in the elimination of nitrogen, urea, ammonia, purins, and the appearance of creatin in the urine. Cretinism and myxedema are cured by its use. Thus all known actions of the thyroid or desiccated thyroid extract are properties of thyroxin (Kendall, Plummer, Janney, Rowntree).

The avidity of the thyroid gland for iodin is explained nicely by the necessity of iodin for thyroxin production. The amount of the iodin in the thyroid is not of necessity proof of its functional activity as its secretion is given off into the blood. The iodin content of goiters is, however, usually decreased. The amount of colloid material in the gland is also no very definite criterion of functional activity. The ultimate function and nature of the colloid remains obscure.

The effect of the thyroid gland on the basal metabolism is marked. Although the pituitary and other endocrine glands may influence the basal metabolic rate to some extent, the greatest regulator of the gaseous exchange is certainly the thyroid. Excision of this gland leads to profound depression of the metabolic rate toward − 40. Administration of thyroid material produces a rise in the metabolic rate to normal. This action is quantitative, according to Plummer, ⅓ mg. of the active substance increasing the metabolic rate 1 per cent. in an adult.

Like all endocrine organs, the thyroid is under the influence of the sympathetic nervous system, with cortical connecting fibers. Recently, important studies of its secretory phenomena have been made by Cannon,[2] also Bensley,[3] who clearly demonstrated the sympathetic control of thyroid activity and also the influence of adrenalin in producing thyroid activity.

It seems rather surprising that the chief function of the thyroid gland has remained rather unappreciated by many. This organ unquestionably exerts a controlling influence upon the renewal and regeneration of cells, also the growth of new tissue. This effect is quite general, as is clearly demonstrated by the widespread degeneration following removal of the thyroid and resumption of growth in cretins

on proper thyroid therapy. A certain confusion in regard to thyroid function has chiefly arisen from ascribing the toxic effects of an overdose of thyroid tablets or of the pathologic gland in exophthalmic goiter to a supposed increase of normal function, so-called "hyperthyroidism." The various data militating against the acceptance of this view cannot be detailed in this summary, but have been previously described by many authors, also recently by the present writer and coworkers[4] (see also sections on Hypothyroidism and Thyrotoxicosis). The conception of the anabolic function of the thyroid gland (Janney, 1915) on the repair and synthesis of the cells accepts also that catabolic processes accompanied by a rise in the gaseous exchange may be simultaneously involved. Thus it is known that a rise in the basal metabolic rate accompanies renewed growth in a cretin, and an increase, not a decrease, in the nitrogen is retained in the body when proper doses of thyroxin are administered. The basal metabolism is probably merely a measure of the total metabolic processes, including both oxidations and reductions caused by the action of thyroxin. Therefore, a simple kinetic theory of thyroid action, such as is implied by the hypothesis of "hyperfunction" in exophthalmic goiter, is insufficient to account for the facts.

Clinical Methods of Examination.—Medical History and Physical Examination.—The family history is of considerable importance, in view of the marked hereditary tendency, as well as the obscure nature of many thyroid cases. But too frequently only a cursive inquiry is made as to the presence of goiter in the patient's family. It is, however, well also to investigate carefully the possibility of residence in a goitrous district, whether abnormally short individuals belonged to the patient's family, whether there is present a family pre-disposition to obesity, especially youthful obesity, a dry skin, scanty hair and eyebrows and brittleness of the nails. If thyrotoxicosis be suspected, change of psyche to the irritable, excited type, heart palpitation and loss of weight should be inquired after, in addition to the classical symptoms of exophthalmic goiter. The possibility of psychoneuroses and insanity appearing in thyroid families should be remembered. In regard to the patient's own history, particular regard should be given to normality of growth, i.e., weight and height at various ages, irruption of temporary and permanent teeth, age when crawling, standing, walking, talking and cleanly habits began. Cessation of growth, otherwise unaccounted for, should always arouse suspicion of hypothyroidism.

In the physical examination, too great attention has sometimes been paid to the thyroid gland itself, without due consideration of the importance of the general signs of disturbed thyroid function. It may be remembered that physical examination of the thyroid gland may be negative, even in severe thyroid disease. The body build, gait, intelligence, state of nutrition should be carefully noted, as well as the special signs described in other sections of this chapter. Too often mild cases of juvenile hypothyroidism escape notice, as the medical

attendant is seeking for the textbook picture of outspoken cretinism. There is always a temptation to neglect complete removal of the clothes in examining such cases. When the diagnosis is obscure, both parents should be examined for possible thyroid disease.

The physical examination of the thyroid is rendered easy by its superficial situation in the anterior cervical region. Inspection in hypothyroid cases may reveal a certain leanness of the neck and prominence of the larynx, or the well-known appearance of goiter. Palpation should be systematic, including the size, texture and mobility of each lobe, as well as of the gland as a whole, and isthmus. Palpation of the thyroid can conveniently be carried out by standing facing the back of the patient. The fingers laid together then readily ascertain the condition of the thyroid by a process of gentle balottement. Thyroid bruits are rarely heard in children's cases.

Examination of the Blood.—A mild anemia is frequently present in hypothyroidism with corresponding decrease of the red-blood corpuscles and hemoglobin. The number of leukocytes is usually unchanged. The differential blood count is, however, of distinct importance, there being present a persistent lymphocytosis and mononucleosis, both in hypo- and hyperthyroid cases. This reversion of the leukocytic formula to the fetal type is in excess of the known lymphocytosis of early life (Kocher and coworkers, Lampe, Liesegang and Klose, Falta, McCarrison).

Estimation of the Basal Metabolic Rate.—The application of basal metabolic studies to the clinical study of thyroid disease has recently been made possible through the development of clinical respiration apparatus by F. G. Benedict and T. Carpenter,[5] also others. At the present writing (1920) basal metabolic rate determinations are becoming extensively used, both in the diagnosis and control of treatment of hypothyroidism and thyrotoxicosis in the adult, following the introductory studies of Du Bois,[6] Means and Aub,[7] Plummer[8] and others. With regard to the young, metabolic studies can at present be conveniently made only in the cases of older children, as the coöperation of the patient is necessary. It is hoped that practical respiration apparatus may be soon developed for infants and small children, as seems likely from Benedict and Talbot's researches. The normal metabolic rate has been determined, by comparison with which the metabolic rate may be found to be depressed to from 10 to 20 per cent. in lighter cases of thyroid deficiency to even approaching 40 per cent. in grave cretinism and athyreosis. In thyrotoxicosis is found a rise of the basal metabolism above normal up to 100 per cent. or even more in the severest cases. The value of basal metabolic rate determinations in the diagnosis and treatment of thyroid cases will be further discussed under the appropriate sections. The basal metabolic rate may be regarded, if not an absolute criterion, yet the most reliable test of thyroid function we at present possess. It has the great advantage of being a physical method, independent therefore of the subjective influence of the medical observer.

The Benedict-Carpenter portable respiration apparatus, the only one now in general use clinically, is fairly simple in its present form, but unquestionably requires experience and reasonable care to insure accuracy. Some simple form of respiration apparatus will, in future, probably prove a necessity in the office of the pediatrician or pediatric clinic.

The Carbohydrate Tolerance.—The thyroid is intimately related to the carbohydrate metabolism. Thus it has long been known that the ingestion of 100 gm. of carbohydrate does not normally result in glycosuria in normal individuals, but frequently is followed by the same in thyrotoxic cases. Conversely, 200 gm. or more of carbohydrate may be ingested by some hypothyroid cases without showing sugar in the urine. These rough chemical tests were usually applied to adults. Recent standardization of the technique of the glucose tolerance test[9] and the coincident observation of the effect of ingested glucose on blood and urine has enhanced its clinical value. The test is applicable to children as well as adults.

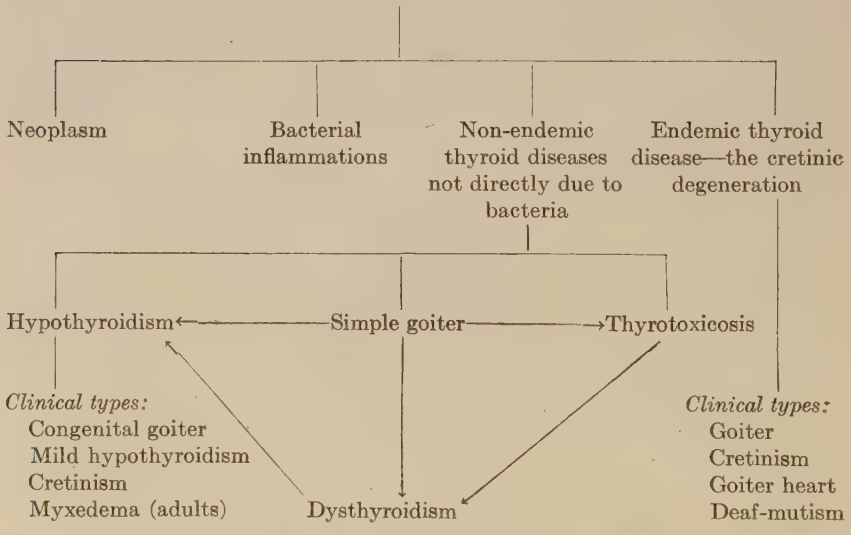
The technique is as follows: 1.5 gm. glucose is dissolved in 3 c.c. water for each kilogram of the patient's body-weight, and a little lemon juice added for palatability. The fasting blood sugar is determined before breakfast, the sugar drink being taken as soon as blood is withdrawn. Subsequently, at hourly or half-hourly intervals, the blood-glucose level is ascertained, the urine being meantime tested quantitatively and qualitatively. A response is considered normal when the blood sugar has returned to normal at the end of one and one-half or two hours from the time when the glucose was ingested, the maximal value being not over 120 to 140 mgm. glucose in 100 cc. blood, and no urinary sugar being found. In hypothyroidism there is frequently hypoglycemia, a low peak to the bloodsugar curve, a delayed return of the curve to normal and no glycosuria. In thyrotoxicosis there is more often a normal or supernormal fasting blood sugar, a supernormal elevation of the blood sugar at the top of the curve, at the end of a half hour or hour, also a delayed return of the blood sugar to the fasting level and glycosuria. Very recent studies[10] have shown that these results are not necessarily present in all cases; also that there is no definitely characteristic blood-sugar curve for thyrotoxicosis in distinction to hypothyroidism. Abnormal blood glucose and urinary response to sugar ingestion may occur in endocrine disturbances other than the thyroid, so that an abnormal blood-glucose curve is simply to be regarded as a general sign of endocrine disturbance. This test has nevertheless its definite value, especially in dysthyroid cases or incipient hyperthyroid cases showing a normal basal metabolism.

Other Tests for Thyroid Function.—The clinical reaction to adrenalin injections has again recently been advocated as a test of thyroid function,[11] a toxic response being elicited in thyrotoxicosis cases. Interest to this reaction has been lent by Cannon's recent discovery of the power of epinephrin to stimulate the secretory activity of the

thyroid. As a positive response to this test is obtained in cases which are obviously negative as to thyroid pathology, this procedure is rather to be regarded as indicating increased reactivity of the sympathetic nervous system. The sudorific action of pilocarpin has also been utilized in European clinics as a test for thyroid function. It presents no obvious advantages.

Nomenclature and Classification of Thyroid Diseases.—Present nomenclature of thyroid diseases is far too vague. Some of the terms in use are still merely descriptive of a prominent symptom, such as "infantile myxedema." In nearly every work on the thyroid gland, a different classification of its diseases has been adopted, an ample testimony to the present state of confusion. In seeking for a clearer conception of thyroid diseases, one turns to etiological factors. Unfortunately, however, neither the etiology of Graves' disease nor the cretinic degeneration is firmly established, so any classification based on causative factors is subject to possible modification. An attempt, however, has been made in the accompanying diagram to represent schematically the chief abnormalities of the thyroid gland.

SCHEMA II.—CLASSIFICATION OF THYROID DISEASES (JANNEY)



In explanation of the terms adopted in this chapter, the following may be mentioned. The treatment of the subject of goiter as a separate disease in clinical textbooks has but added to the present confusion, as the term goiter, properly considered, merely designates a swelling of the thyroid. Since recent experimental and histopathologic studies render it likely that such hypertrophy of this organ is merely the first reaction to increased demand upon it from without (such as goiter of pregnancy), or from decreased ability of the thyroid to meet the normal demand for its hormone (goiter of hypothyroidism, or thyrotoxicosis), surely to regard goiter as a clinical entity is scarcely

indicated. The subject of "Endemic Goiter" is therefore treated under "*The Cretinic Degeneration*," as goiter, in this case, is but an early or slight expression of the same. A separation of "Congenital Goiter" from other symptoms of hypothyroidism seems no longer advisable in view of McCarrison's recent experimental studies. The term "Toxic Goiter" is ambiguous when applied as synomonomic with Graves' disease, as it is now known that goiter may arise from a toxic cause as well as produce a toxic effect on the organism. As various thyroid diseases are congenital, there seems no ground for such a designation as "Congenital Cretinism." The term "Simple Goiter," for want of a better one, appears in the accompanying schematic classification of thyroid diseases, merely to illustrate the fact that a thyroid swelling may (1) precede hypothyroidism, or (2) be followed by thyrotoxicosis (Wilson, Plummer), or (3) the dysthyroid syndrome. These possibilities are indicated by arrows on the schema.

The designation "Hyperthyroidism" does not appear in the schema. In view of recent important studies (see discussion under Thyrotoxicosis) the older classical contrast made by Kocher between hypo- and hyperthyroid symptoms had best be no longer perpetuated by modern terminology. The term *Thyrotoxicosis* is, therefore, adopted, as it is coming into use to express the peculiar syndrome of toxic symptoms due to a toxemia of thyroid origin, whether such symptoms be slight (often designated as *Hyperthyroidism*) or severe (*Graves' disease, Basedow's disease, Exophthalmic goiter*).

It is preferred to apply the designation *Hypothyroidism* to all forms of thyroid deficiency *per se* in distinction to *The Endemic Cretinic Degeneration*, probably of mixed etiology. All types of hypothyroidism, from the mildest, exhibiting only goiter, to the severest merge into each other, so that such a designation as *Cretinism*, probably derived from the Rhineto-Roman root, "cret," a dwarf, or "cretin," tiny, is not universally applicable. The appellation, cretinism, however, is very descriptive of pronounced clinical manifestations of severe hypothyroidism and may well be retained to designate this classic clinical syndrome, whether occurring endemically or sporadically. "Infantile or juvenile myxedema" is a rather unfortunate term, as it relates only to the subcutaneous swelling, therefore but to one symptom. The same may be said for "myxidiocy" (German, myxidiotie). The terms "athyreosis" and "hypothyreosis" may be criticized, as the developed clinical symptoms may be nearly identical in either case. This attempt at classification on a pathological, anatomical basis seems unnecessarily forced. These terms had best be dropped. The term *Dysthyroidism* is retained to describe a common type of case showing a combination of thyrotoxic and hypothyroid symptoms. Dysthyroidism may be regarded as a transition stage through which a few cases of thyrotoxicosis pass to develop finally the symptoms of hypothyroidism. Arrows in the schema illustrate this inter-relationship. The *Endemic Cretinic Degeneration* (Falta) has never been successfully separated from

thyroid diseases, although other etiologic factors are likely concerned. Until these latter should be possibly shown to be of sufficient importance to warrant a separation, we may with fair right describe this group under thyroid diseases with due reserve, acknowledging, however, a common etiology by including under the cretinic degeneration the clinical types, endemic goiter, endemic cretinism, goiter heart and endemic deaf-mutism. The term goiter heart (see text) had best be dropped as a nosological entity, in as much as this condition is but a symptom of certain thyroid diseases, though particularly frequent in endemic regions.

CONGESTION, INFLAMMATIONS AND NEOPLASM

Congestion.—The thyroid gland is unusually well supplied with blood vessels, which is probably due to the importance of its secretion for the human economy. This fact, together with its anatomical location, predisposes it to transitory congestions. Such may be seen on birth, subsiding within a short time. The wearing of a tight neckband or collar, sudden excitement and epileptic attacks are other etiological factors. Thyroid swelling may occur from a cramped posture during sleep. As congestion of the thyroid may be readily superimposed on a struma of inflammation, diagnosis of congestion may only safely be made when other causes of swelling are excluded.

Inflammations.—Acute inflammation as a primary condition is extremely rare. It may follow trauma, birth injury or develop without apparent cause. Secondary thyroiditis may occur in the course of various acute infections, such as measles, mumps, diphtheria, scarlet fever, typhoid and malarial fevers. Such inflammation is characterized by the presence of bacteria which have been recovered from the gland. The symptoms of inflammation are present. Usually the application of cold produces a quick recovery but a few cases go on to abscess formation and very rarely to atrophy. Although not included under thyroid inflammations, it may be noted that the pathological findings in both thyrotoxicosis and certain thyroid glands in hypothyroid subjects exhibit a histo-pathologic picture of a chronic inflammatory process.

Tuberculosis and syphilis practically never attack the thyroid primarily.

Neoplasm.—Neoplasms of the thyroid are medical curiosities in children and indeed rare in adults. The single case known to the author was that of carcinoma of the thyroid in a child reported by Demme.

NON-ENDEMIC THYROID DISEASES

Thyrotoxicosis

Definition and Nomenclature.—Thyrotoxicosis may be defined as a disease exhibiting toxic and other symptoms caused by an abnormally functioning thyroid gland. The condition is characterized

in typical cases by goiter, exophthalmos, tachycardia, tremor of extremities, and rise in basal metabolism. *Thyrotoxicosis* is preferred to exophthalmic goiter as a general designation for this disease, as neither exophthalmos nor goiter are necessarily present in this affection. The synomic terms "Graves' disease" and "Basedow's disease" are best avoided in pursuance of the modern tendency towards a descriptive nomenclature. As the entire conception of "hyperthyroidism" as opposed to hypothyroidism is very questionable (see under "Pathogenesis"), the former designation has not been adopted in the present treatise.

Etiology.—Thyrotoxicosis occurs much less frequently among children than adults. Thus, Sattler found but 184 cases occurring before the fifteenth year in a series numbering 3477. The incidence is greater in females, but less so than after puberty. Young children are very rarely affected, the incidence increasing with advancing age. White Clifford has reported the case of a breast fed child. Only 11 of Sattler's 184 children cases were five years of age, or under. A familial influence is traceable in some cases. There may be obesity, or a psychoneurotic ancestry. A number of instances are recorded in the literature of the development of the disease in the offspring of thyrotoxic mothers. Certain children of the same parents may show hypothyroid, others thyrotoxic symptoms.

A number of cases have developed after fright, violent emotion, etc. Thyroiditis or contiguous inflammations, acute and chronic infections of general nature may be followed by thyrotoxic symptoms (Stanton, etc.). Such are sinusitis, tonsillitis, influenza, rheumatic fever and tuberculosis. Mackenzie has demonstrated the etiologic influence of non-hygienic living. The combination of nutritional, psychic and infectious factors is very important. The prevalence of gastro-intestinal disorders in thyrotoxic patients is established and regarded by McCarrison of etiologic significance.

Pathology.—So few studies in children have been made that the following data have been drawn from adult sources. The gland exhibits an irregular hyperplasia with increased epithelial cells and stroma with loss of colloid. Alveoli of all sizes are interspersed with fibrous bands. The pathological-anatomical changes are roughly proportionate to the severity of the cases. For details see the descriptions of Hirschlaff, Ehrich, Hansemann, etc., and the American authors, W. G. MacCallum, Ewing, Wilson, MacCarty, Marine and Lenhart, *et al.* The iodin content is reduced in amount (Kendall), and varies inversely with the degree of hyperplasia (Marine and Lenhart).

The fact that thyrotoxicosis is a general disease must not, however, be disregarded. Lymphatic swellings are common. The finding of thymus hyperplasia is frequent, but an etiologic relationship has not been established. The hypophysis and spleen may also be hypertrophied and degenerated. Atrophy, degeneration, pigmentation, petechial hemorrhages in various parts of the sympathetic and central

nervous systems occur. Askanazy has drawn attention to fatty degeneration and atrophy of the musculature, also cloudy swelling and degeneration of the viscera. Stunted growth may occur in young subjects, with imperfect ossification and delayed appearance of the long-bone epiphyses.

Pathogenesis.—In spite of much patient research the pathogenesis of thyrotoxicosis remains ultimately obscure. At the present time the various theories as to pathogenesis have narrowed down to two: That accepting an increased functional state of the thyroid, *i.e.*, "hyperthyroidism," and secondly, an altered toxic secretion, as ultimate etiologic factors. Full discussion of these theories is here impossible. Reference may be made to the writings of Sattler; Lampe, Liesegang and Klose;[12] Falta, Ord,[13] McCarrison, Howard,[14] West,[15] Dock,[16] Plummer,[17] Janney[4] and others. The chief facts behind the hyperthyroid theory are the clinical antithesis between the thyrotoxic and hypothyroid states (Kocher), the excellent results of thyroidectomy in Graves' disease, the artificial production of its symptomatology by thyroid tablets (Notthafft's classical case, etc.), and the finding of hyperplasia in thyrotoxic goiters. Careful clinical analysis has, however, shown that the contra-distinction of "hyper" and "hypo" thyroid symptoms is merely superficial, that symptoms of both these categories may be frequently exhibited by the same individual(*dysthyroidism*). Again, thyrotoxicosis may be followed by myxedema. Improvement after thyroidectomy is no proof of hyperfunction, as the same result would be expected after the partial removal of a gland producing a toxic substance, perhaps incompletely or aberrently synthetized thyroxin, thus giving opportunity for subsequent normal hyperplasia and restored function in the portion of the thyroid left intact. Artificial production of hyperthyroidism and even ophthalmos by thyroid substance is not a proof of the correctness of the hyperthyroid theory, as the breakdown of excessive amounts of thyroxin in the body may, through production of toxic catabolic products, cause the symptoms primarily or secondarily, by stimulating the thyroid to production of an abnormal secretion. Thyroid hyperplasia is, however, according to Marine and Lenhart, McCarrison, etc., merely a compensatory reaction to thyroid insufficiency, and is found in cases of hypothyroidism and even in apparently normal individuals (Hale, White, etc.). It may also be added that, according to the hyperthyroid theory, we must accept "hyper-functioning goiters" and "hypo-functioning goiters," clearly a paradox.

The theory of a qualitatively altered thyroid secretion in thyrotoxicosis accepts (1) the presence of a toxemia in all or in part of thyroid origin, (2) altered function of the thyroid. This view affords best correlation to the known clinical and pathologic facts. In thyrotoxicosis there is present (1) goiter, or at least microscopic hyperplasia of the thyroid, (2) a series of toxic symptoms, (3) symptoms referable to thyroid hypofunction. With regard to the significance of the thyroid swelling, McCarrison calls to attention that all thyroid pathologic

processes (barring neoplasm and acute inflammation) are "essentially the same, greater or less degrees of hyperplasia followed by greater and lesser degrees of fibrosis and atrophy." Goiter, i.e., thyroid hypertrophy, presumes in all cases a *need* for increase of thyroid function (puberty, pregnancy, etc.). The toxic symptoms are mainly referable to an over-stimulation of the vegetative nervous system, which may be due (1) to a primary intestinal and bacterial toxemia, or (2) to the toxic action of an imperfectly or aberrently synthesized thyroxin (Janney), produced by the thyroid through injury caused by the primary toxemia or over-stimulation of the thyroid's sympathetic fibers by shock, fright, adrenalin, etc. The presence of hypothyroid symptoms in thyrotoxicosis remains to be accounted for. The hypothesis of a qualitatively altered secretion produced by a goitrous thyroid affords an easy explanation for these puzzling manifestations which have always rendered the acceptance of the hyperthyroid hypothesis most difficult. As, then, the process of atrophy and fibrosis which follows the preliminary toxic hyperplasis continues, signs of hypofunction may become increasingly frequent until there intervenes the clinical picture of dysthyroidism, i.e., the mixed picture of thyrotoxicosis and hypothyroidism. Myxedema following Graves' disease may finally develop, as total fibrosis of the gland slowly takes place.

Symptomatology.—Thyrotoxicosis in children is generally less severe than in adults. But a few of the classical signs, such as goiter, exophthalmos and pulse frequency may be present. Even these signs are usually mildly exhibited. The clinical manifestations may be conveniently grouped as follows: (1) Local, (2) toxic, (3) signs of disturbed thyroid function.

Group 1 includes goiter, usually soft, elastic and rather symmetrical. In 4 per cent. of cases it is absent. Severer symptoms, such as stridorous respiration, voice alterations, engorged veins, and bruit are rare.

The toxic symptoms, Group 2, may be described as the results of a general hyperstimulation of the sympathetic and, to some extent, of the central nervous system. The skin is warm, hyperemic and moist. *Tâche cerebrale,* nervous tremor of extremities, twitching, rarely true choreaform movements (10 cases in the literature—Sattler), also frequently rise of temperature and respiratory rate occur. The tachycardia is usually not high, only in 20 per cent. of cases over 125 per minute. Visible precordial and carotid pulsation is not uncommon. Cardiac enlargement and mitral incompetency may rarely follow. Exophthalmos, i.e., protrustion of the eyes, causes the expression of fright so frequent in these cases, and is probably due to a contraction of the Landström ring muscle. The eye-ball is shining, due to excessive lachrymation, and pupils dilated. Special eye-signs are the following: Stellwag's sign, a widening of the palpebral fissure; von Graefe's sign, a failure of the eye-lids to follow movements of the eye-ball; Möbius' sign, lack of normal convergence of the eyes' axes on fixing a near object. Other optic signs of trivial importance have

been described. Gastro-intestinal disturbances include loss of appetite, vomiting, hypochlorhydria and diarrhea. Very frequently thyrotoxic children become nervous and irritable, especially marked in those of psychoneurotic families.

The last group of symptoms, those directly referable to abnormal thyroid function, are so over-shrouded by the toxic that they are frequently overlooked. Though marked retardation of growth is rare, the ossification of the epiphyses may be delayed and the long bones be gracile and thin. The writer has observed ununited fracture evidently resulting from this cause. Muscular weakness, a symptom emphasized by F. v. Miller, if looked for is found very frequently. Under nutrition may be quite absent in light cases, but, however, quite marked in the severe. Affected children are usually delicate of form and limb. Rare symptoms falling in this category are cutaneous atrophy, scleroma and pigmentation, myxedematous deposits about the eyes or lower extremities. The nails may be seamed, thin and small, as in hypothyroidism. The hair may be dry and fall out. The mixture of toxic with hypothyroid symptoms may become so marked that very rarely the condition may show the characteristics of dysthyroidism, as observed in adults. Such cases have been described by F. E. Batton, S. Watson, von Ulrich. It is probable that true hypothyroidism may develop in children just as in older individuals after thyrotoxicosis, but this process usually requires many years.

The blood in thyrotoxic patients resembles that of hypothyroidism, suggesting a similar etiology, i.e., abnormal thyroid function. Few observations have unfortunately been reported for children who likewise normally show some of the changes to lesser degree observed in the leukocytic formula. There is a decrease in the percentage of polymorphonuclear cells, increase in the lymphocytes or large mononuclears. By some observers eosinophilia has been reported.

Metabolism of Thyrotoxicosis.—But very few metabolic studies of thyrotoxicosis in children have been recorded. The following data have been chiefly supplied from observations of adults: The *basal metabolism* is elevated above normal in thyrotoxicosis, and falls again on successful treatment (Plummer, Du Bois, Means and Aub). The *protein metabolism* shows an increase in the nitrogen output and all products derived from protein and creatinuria, as a result of the general stimulation of catabolic processes which are similar to those observed when thyroxin is experimentally administered. The carbohydrate metabolism may be also abnormal. Alimentary glycosuria is common in severe cases. The blood sugar may be normal or elevated. The blood-glucose curve is abnormal according to recent studies by H. R. Geyelin,[18] Janney and Isaacson,[19] and McCaskey.[20]

Diagnosis.—No disease is more typical than marked thyrotoxicosis, exhibiting the three cardinal symptoms of goiter, exophthalmos and tachycardia. Only the mild cases give diagnostic difficulty, which careless observers have confused with hysteria and neurasthenia.

"Goiter heart" is an unsafe diagnosis. A thorough physical examination is all that is really essential. The clinical symptoms are, however, not as indicative as the basal metabolic rate of the real severity of the underlying metabolic disturbance. It is hoped that this means of diagnosis may soon become generally applicable clinically. It should not be overlooked that a mild thyrotoxic state may be due to toxemia of tuberculosis or other chronic infections, also helminthiasis.

Prognosis is generally more favorable than among adults. According to Sattler's classical monograph, 30 per cent. of children fully recovered, the majority, however, incompletely. The mortality is only about 4.5 per cent.

Treatment.—Three principal modes of treatment are in vogue at present, and may be applied in the order indicated: (1) Rest and hygiene; (2) Roentgen-rays; (3) surgery.

Rest and hygiene occupy a particularly important place in the treatment of thyrotoxicosis in children, on account of the fact that most cases are light enough to benefit thereby. This therapy would be more fruitful of results if it were carried out more thoroughly than is usual. A complete rest in bed, combined with mild sedatives, massage, careful avoidance of all excitement, is often followed by a cure. In less severe cases, the avoidance of rough games, lightening of school tension, a rest period in the middle of the day and a long bed-rest at night may suffice. The diet in thyrotoxicosis should be plentiful to make up for the increased metabolic activity. According to the author's studies, a mixed diet of high caloric value is of most value. It should be remembered that the patient's requirements may be greatly in excess of the normal. The caloric content of the diet should, therefore, in selected cases be calculated. The possibility of intestinal toxemia, as a cause of thyrotoxicosis, should lead to especial study of the gastro-intestinal tract and correction of colitis, etc.

The Roentgen-ray treatment of thyrotoxicosis has recently acquired a new importance through the work of Means and Aub[21] with adults, who, with careful observation of the metabolic rate, have come to the conclusion that it is to be preferred to surgery. Irradiation of the thyroid and perhaps also the enlarged thymus may be resorted to, if a careful rest and dietetic care prove ineffectual. Cases have, however, been made worse by injudicious Roentgen-ray treatment.

Thyroidectomy is very seldom necessary in children in view of the distinct mortality. Operation may, however, become advisable. As the thyroid is an organ controlling growth and tissue formation, probably not as much of the gland should be removed as in adult cases of the same toxicity, for fear of inducing hypothyroidism and cessation of growth.

Organotherapy.—Typical thyrotoxic cases usually respond with still greater toxicity when thyroid is administered. Reports, however, on the reduction of toxic goiters by iodin or thyroid tablets are not uncommon, but great caution must be observed. It would be better to reserve thyroid treatment for cases showing distinct signs of deficient

thyroid function, obesity, myxedematous swellings, etc., and then make a trial with minimal doses.

Hypothyroidism in Children

Definition.—This disease may be defined as the sporadically occurring clinical syndrome due to deficiency of the thyroid hormone. For synonyms and relation to other thyroid diseases, see Sections "Nomenclature and Classification of Thyroid Diseases" and "The Cretinic Degeneration."

Etiology.—All factors lowering the functional activity of the thyroid are to be included. Heredity plays a rôle insufficiently emphasized in present textbooks. Cases of marked hypothyroidism in mother and child, such as MacIlvaine's, are infrequently met with, as pregnancy is then rare. Many mild cases of thyroid deficiency are, however, markedly hereditary. C. Herrman[22] described three sporadic cretins in one family. Barrett[23] reported even 62 members of one family with thyroid anomalies. Janney and Henderson[10] have reported three hypothyroid families in 18 consecutive cases. Infectious diseases, such as scarlet fever, measles and acute enteritis, are probably etiologic factors, but for children, this has not been certainly demonstrated. Various writers, however, have observed in adults the development of hypothyroidism after acute infections (typhoid fever, rheumatic fever) and chronic intoxications. McCarrison[4] considers intestinal toxemia to play an important part in the development of cretinism. His experimental production of hairless and goitrous offspring in goats by feeding them feces from goitrous men are very significant. Direct trauma or goiter operations are rarely followed by hypothyroid symptoms. Infrequently thyroid deficiency may follow thyrotoxicosis Goitrous degeneration of the thyroid may be both a cause and accompaniment of hypothyroid symptoms.

Pathology.—In considering the pathology of hypothyroidism, certain generalities may first be mentioned. The function of the thyroid hormone to control the building of new tissue, whether by replacement and repair, is probably exerted upon every cell of the organism. Therefore the most diverse and widespread pathologic changes follow deficiency of the thyroid. Adults suffer less than do the young, as growth has been already attained. There is, however, no fundamental difference between the pathology of cretinism and myxedema. Indeed, cretins may exhibit all the lesions, including those of the skin, seen in myxedema of adults. It is probable that growth is inhibited in *myxedema adultorum* in those tissues capable of regeneration in older individuals. This is likely as it is known that severed nerves regenerate more slowly in thyroidless animals.

Congenital absence of the thyroid gland (Athyreosis, Thyroaplasia) has been carefully studied by Pineles. Serial histologic sections have demonstrated the complete absence of the thyroid in 15 cases (E. Thomas). In many instances in which the gland was thought to be

absent by physical examination, evidence of functioning tissue became manifest on more careful study. The thyroid may gradually involute during the early years of life, with resulting hypothyroid symptoms appearing usually between the fifth and sixth years. Few careful studies of the histopathology of these youthful cases have been made. According to the post-mortem and histologic studies of the English Myxedema Commission and other observers, the retrograde changes consist, in the adult, of the slow substitution for the glandular tissue of connective tissue with round-cell enclosures. The changes are aptly compared by Hadden to those of chronic diffuse nephritis or cirrhosis of the liver. The gland of hypothyroidism is frequently goitrous and usually markedly degenerated.

Skeletal changes are usually marked and may set in very early. They are ably described by Wieland (see bibliography). Dieterle's case of a four months old child suffering from athyreosis presented precisely the bony development of a newborn infant. The epiphyses are greatly delayed in their development and attachment to the diaphyses (Falta). Structural epiphyseal changes are present, characterized by a decrease in the cartilage proliferation zone and the development of a peculiar bony partition closing off the diaphysis. The long bone shafts show narrowing of the marrow cavity and osteosclerotic changes. The skull is thickened but exhibits an open great fontanelle, which may persist for many, even 20 years (Bourneville's case). The entire facial bones and *basis cranii* are undeveloped, producing the saddle nose, small eyes and prominent forehead of the cretin. The mandible is likewise gracile, the milk teeth appear late and may be persistent; the permanent are small, abnormally located, erupt late, decay early. The head is disproportionately large, the bony development and epiphyseal closures being even more below the normal than the body stature would indicate.

The pathology of the various body organs of severe hypothyroid cases in children has not yet been fully investigated. From the complex symptomatology widespread degenerative lesions may be expected. Not only are cretins child-like in size and intelligence, but their tissues differ from those of normal children.

The nature of the myxedematous swellings is not altogether clear. Some investigators claim the mucilaginous deposits to be mucin, while others believe them to only resemble this body in staining power and reactions. These peculiar deposits have been found aside from the skin in the uvula, tonsils, larynx, female genitalia, about the anus, in tendons, salivary glands, kidney, muscles, brain, etc. A modern chemical study of the myxedematous substance is indicated. Other pathologic features are most conveniently described with the clinical symptoms.

Symptomatology and Course.—Development of the Symptoms. The severity of the clinical symptoms varies directly with the amount of functional injury of the thyroid gland, but even children with congenital absence of this organ may undergo a certain degree of devel-

opment, probably through the influence of other endocrine organs upon growth, notably the pituitary.

In the following description of the symptoms of hypothyroidism in the young, no distinction is attempted between athyreosis, cretinism and infantile myxedema, inasmuch as these conditions, viewed clinically, vary only in degree or merge into each other. It should be emphasized that only typical and severe cases show all or most of the changes recorded, also that recent studies have shown that the lighter are probably more numerous than has been supposed, and frequently exhibit but few stigmata (see below).

Even when the thyroid is congenitally absent, the newborn develop the signs of thyroid deficiency but slowly. This has been ascribed to the protective action of the mother's milk (Kocher). The symptoms often do not appear until the third or fourth month. Growth slows or ceases, particularly in height; myxedematous swellings appear in the mucous membranes and subcutaneously; the child fails to show normal mentality, and the other symptoms follow. Much more frequently development is normal for the early years, thyroid deficiency slowly coming on with the gradual loss of the thyroid tissue. Such cases are more frequent in the fifth and sixth year. Retardation of growth may or may not be progressive as time goes on. At times it is extreme, Curling reporting a case measuring 26 in. in height at the twentieth year, Telford Smith, 30 in. at the sixteenth year. Growth anomalies in hypothyroidism are ably described by Wieland. Excellent clinical descriptions with illustrations have been given by numerous authors including F. Siegert, Falta, Wieland, Osler and Dock (see bibliography).

General Symptomatology.—The cretin is short, fat and stupid; creeping, standing and walking awkwardly. The head and face are round. The forehead has transverse wrinkles. The hair frequently is scanty, brittle and dry, and defective in pigment. The ears are usually large and hearing defective. The under development of the *basis cranii* and facial bones gives the appearance of a protuberant forehead, deep-set small eyes, small saddle nose, flaring, upturned nostrils, exuding nasal secretion. The eyebrows, particularly the outer third, may be absent or scanty. Either or both eye-lids and face generally may show myxedematous swellings. The malæ are unusually prominent. The mouth and lips are large and frequently open, from which the huge, tooth-marked, furrowed tongue may protrude. There is often a double chin caused by defective mandibular development, myxodemic swelling and forward carriage of the head. Garrod calls attention to the characteristic grin of the cretin, but the pale pasty face frequently is fixed in a stupid stare, accompanied by a peculiar angry, bestial expression. The bodily movements are slow and awkward. The child stands with feet apart seeking support, walking with waddling gait and sitting silently, unless disturbed by others. Obesity, complicated or not by myxedematous swelling, is

an important symptom. It may be strikingly in evidence when other hypothyroid symptoms are present.

Examination of the mouth and throat shows pale, often swollen mucous membranes, narrow, high-arched palate, at times large uvula (requiring amputation in one of my own cases), swollen tonsils, frequently adenoids. The voice is raucous and hoarse, caused by swelling of the mucous membranes of the vocal cords. The milk teeth erupt late, frequently not until the twentieth month. They appear irregularly, are small and often carious. The same applies to the permanent teeth which may indeed not appear until the third decade. In thyroaplasia, no teeth whatever may erupt. The permanent teeth are frequently widely and irregularly spaced, small, deficient in enamel, therefore wearing down and decaying rapidly. Orthodontial deformities are common.

The neck is short and thick, the thyroid fullness being absent. The *thorax* is short in proportion to the abdomen. There is usually a backward curvature of the dorsal vertebræ, but the lumbar vertebræ curve forward, adding to the well-known pot-belly of the *abdomen*, which is caused by fat, weakness of the abdominal walls, and intestines distended by feces and gas. The umbilicus is protuberant. *The limbs*, particularly upper arms and thighs, are short and at times bowed. The muscles are flabby and small, though the myxedematous swelling may give the false impression of good musculature. The hands are cold, small, spade-like or claw-like. This is very characteristic. The feet show similar changes; flat-footedness is common.

The skin is coarse, frequently thickened, dry, cold, cyanotic and hairless; even the lanugo may be absent. Perspiration is deficient. Itching may be complained of. Hair changes of puberty are delayed or absent. The skin may collect in folds about the neck and buttocks. Soles of feet and palms may show epidermal thickening and scaling. Nail as well as skin anomalies are characteristic phenomena and should be looked for carefully in doubtful cases. The nails may be small, thin, soft, seamed and brittle. Myxedematous swellings may involve the entire cutaneous and mucous membrane surfaces, but particularly affect the face, dorsa of hands, and feet. This symptom, however, may be entirely absent, the afflicted child then betraying a frail and emaciated frame. Skin diseases are frequent, particularly eczema and psoriasis; but leukodermia, ichthyosis and scleroderma are frequently observed. The writer has encountered a father and two children, all of whom had a dry eczema and mild hypothyroid symptoms. Cures of these skin diseases are reported to have followed thyroid medication.

The Digestive System.—Appetite is usually described as voracious, due probably to the animal-like manner with which cretins devour their food. The actual amount of food taken, however, has been repeatedly observed by the author in metabolic experiments to be less than normal, when measured by the caloric and nitrogen intake. Absorption of food from the alimentary canal is defective. Gastro-

intestinal disturbances, particularly constipation, are frequent. The liver may be enlarged (Falta). The bowels, in severe cases, may be incontinent, due to defective mentality.

The Genito-urinary System.—The kidneys, in common with all organs of the body, may show degenerative changes, albumin and tube casts being in the urine and disappearing on proper thyroid treatment. Functional renal studies have been reported by Bowen and Boothby,[25] only in adult cases. Improvement ensued on thyroid treatment. Thyroid deficiency is a cause of incontinence and the nocturnal enuresis of children (L. Williams).[26]

The internal and external genitalia are frequently small and stunted. Undescended testicle may occur. The labia may fail to meet or be swollen by myxedematous deposits. Puberty and the secondary sex characters may be absent or greatly delayed. Amenorrhea or menorrhagia are common.

The nervous system suffers severely. All grades of impairment of the psychic functions, from complete idiocy to the slightest, may be present. The cretin baby begins to observe its surroundings, talks, sits, stands, walks and learns to play at a later age than normal. Often the mentality in later years is limited to a few basal concepts, such as expressions of hunger, thirst, anger, fear, etc. The psychic disturbances may be irritative as well as depressive. Thyroid deficient children may be extremely irritable, scream at little provocation, and tend to wakefulness, but the writer has but once observed among sporadic hypothyroidism in America the severe nervous type with diplegia and other grave symptoms described by McCarrison in endemic Indian areas. However, the awkward, waddling gait, slow incoördinated movements may possibly result from an affection of the motor and sensory areas and tracts.

The special senses are severely affected. Falta has ably discussed the disturbances of hearing in cretinism. Although the organ of hearing may be developed and function even when the thyroid is congenitally deficient, *deafness*, which may be complete, is a very frequent symptom of hypothyroidism. There is no unanimity of opinion as to whether deafness is chiefly due to possible myxedematous thickening of the mucous membrane of the middle ear, or is rather to be regarded as cochlear or cortical deafness. *Mutism* is most common when hearing is badly affected. Articulation may vary from the emission of a few unintelligible sounds to the normal. The power of conversation is, of course, inhibited also through under-development of the higher cerebral centers. Vision may be deficient. Taste and smell are less commonly affected than the other special senses. The tactile sense may be lessened by nerve lesion or the myxedematous tissue. McCarrison mentions the scars from burns seen in Himalayan cretins.

Affection of the *sympathetic nervous system* leads to the persistently slow pulse of the hypothyroid individual. This symptom is present in 81 per cent. of cases (Janney and Henderson). Bradycardia,

without obvious cause, in the case of a sick child, should lead to a search for hypothyroid stigmata. The circulation is sluggish, the skin cyanotic, the extremities cold. Such children feel the cold extremely and are bundled in heavy clothing. The body temperature is subnormal, and is less liable to minor fluctuations than is usual in childhood. All glandular activities are inhibited, saliva, sweat and sebum being deficient. Respiration is markedly and persistently slowed. Respirations of six per minute have been reported.

The under-development of the *bones* has been discussed in the pathologic section. A study of the skeletal changes is very important clinically. Roentgenologic studies should be made in each case. The cartilages and tendons are relaxed and infiltrated. Hertoghe regards as very characteristic "the sensation like the crackling of snow" felt over the knee joint. Lordosis, scoliosis, bow-legs, knock-knee and flat-foot are common. Tendon contractures may, however, occur.

The Respiratory System.—Catarrh of the nose and pharynx is common. Hay fever and asthma are not infrequently based on endocrine disturbance (Selfridge, Piness *et al.*). Hypertrophied tonsils and adenoids are frequent and often grow again in hypothyroid children after excision. Such swellings may shrink on thyroid treatment. This should be remembered by nose and throat surgeons. The general lessened resistance of subthyroid individuals is well illustrated by their tendency to respiratory infections. Dyspnea and cyanosis may be present.

The blood changes in thyroid disease have been studied by Kocher, Falta, McCarrison and others. Corresponding to the interruption of the development of the bone-marrow, the blood picture of children is arrested or tends to revert to fetal type (Meunacher). Both the red blood-cells and hemoglobin are reduced correspondingly. There is usually a leukopenia of 3000 to 6000 white cells. The leukocytic formula is characterized by great reduction of the polymorphonuclear cells which may reach less than 20 per cent. The lymphocytes increase correspondingly and are present in greater numbers than is usual for the age of the child. A mononucleosis is the most characteristic change. Eosinophilia has been claimed by some writers. It is not constant. Other features of the hypothyroid blood are decreased coagulability, causing epistaxis and menorrhagia, reduction of the oxyhemoglobin and increased toxicity.

Mild Hypothyroidism in the Young.—Far more important to the practitioner of medicine than the classical symptomatology of cretinism is ability to recognize the mild forms of thyroid deficiency, for such cases are very frequent, while the severe cases are rarely encountered. "Masked" hypothyroidism has been classically described by Hertoghe, Leonard Williams, and others. This condition, though often obscure enough, is perhaps the most common endocrine dystrophy of children or adults. McCarrison aptly remarks: "One has but to observe the passers-by in the streets to notice the great frequency of Hertoghe's 'eyebrow-sign,' for example. Although this

sign may not be confined to subthyroidic states, it indicates the necessity for the search for other evidences of thyroidal incapacity. Insomuch as it is a sign which cannot be missed, its presence should immediately recall the condition—hypothyroidism—to the mind."

Difficult as the mild case of myxedema may be to recognize in the adult, mild hypothyroidism in the young may be still more difficult. All gradations are present, from those showing unmistakable growth, skeletal, psychic, and other signs and symptoms previously enumerated, to others having only one or two slight symptoms. Many of the manifestations are possibly due to other causes; for example, malnutrition, vitamin starvation. The combination of several suspicious symptoms is very important diagnostically. Certain signs of thyroid deficiency are more persistent than others. Among them, inhibition of growth is most important. A baby whose diet is properly managed and still fails to grow should immediately be suspected of thyroid deficiency. Parents of these children frequently report, "The baby eats and eats, but doesn't grow." Growth may be greatly retarded without any obvious stigmata of thyroid deficiency. Slight retardation in mental development is often only ascertainable by close observation and exact questioning of the parents. The infant is slow to learn to balance its head, to sit up, to smile and talk. Both extreme placidity of disposition and drowsiness, as well as apparently causeless irritability, may be present. There is a peculiar reticence in older hypothyroid children to describe their own sensations, due to sluggish mentality (L. Williams). This author likewise emphasizes the important symptom of mental and muscular fatigue. Children with hypothyroidism are disinclined to romp and play, and may be likened in this respect to the cardiac who is a quiet, silent child. The head shows delayed closure of the fontanelles; the complexion may be pasty; the face usually bears some slight stigmata, if carefully observed. The nose may be saddle, with visible nostrils, and slight myxedematous puffiness resembling nephritic edema may be detected beneath the eyes. The tongue and lips are frequently large; mouth breathing and snoring may occur from the presence of adenoids and enlarged tonsils.

Metabolism of Hypothyroidism.—Since the pioneer studies of Magnus-Levy, it has been known that cretins absorb less oxygen and produce less carbon-dioxide than do normal individuals, the basal metabolic rate being depressed. These studies have been amplified and verified by various European and American investigators (see "Clinical Methods of Examination," etc.). The metabolic rate usually varies with the severity of the clinical symptoms. In complete loss of function of the thyroid, a rate as low as −40 may be discovered. Milder cases exhibit higher metabolic rates. The basal metabolism, however, may be much lower than the clinical symptoms would suggest. In such cases it may become of diagnostic value.

The nitrogen metabolism in hypothyroidism has been studied experimentally and clinically by Janney and Isaacson.[27] Nitrogen balance experiments demonstrated the very low nitrogen excretion.

The urea, ammonia, creatinine and phosphates are present in the urine in normal relationship to the nitrogen. The purins are markedly decreased. The abnormal presence of creatine is remarkable (Shaffer, McCrudden, Greenwald). Magnus-Levy and others have endeavored to account for the generally reduced metabolism of hypothyroidism as due to sluggish absorption from the intestinal tract. It was found, however in actual experiments by the writer that food, as judged by the nitrogen excretion, was as rapidly absorbed and eliminated by thyroidless individuals as under normal conditions.

Keeping in mind that the chief function of the thyroid is the control of the growth and regeneration of the tissues, it is likely that the reduced nitrogenous and basal metabolism of the cretin is rather an expression of a compensatory and sparing reaction of the organism. As the normal metabolic repair and regenerative processes cannot be properly carried out because of the thyroid deficiency, the destructive processes are inhibited with consequent decrease in the elimination of total nitrogen, purins, and a fall in the gaseous exchange. Cretins take less food than normal children as they cannot properly assimilate it.

For the results of thyroid treatment as affecting the metabolism, see under section on "Treatments."

Diagnosis of Hypothyroidism.—The diagnosis of typical cretinism is obvious from inspection of the child. Mild cases present more, at times great, difficulty. If it be remembered, however, that thyroid deficiency affects all organs and tissues, and that certain symptoms, particularly when occurring in combination, are characteristic, fewer mistakes in diagnosis will be made. In hypothyroidism, retardation of growth is found in association with mental abnormalities and other distinctive signs. Hair, skin and nail anomalies are nearly always present. The face, teeth and fauces seldom escape, being the seat of at least minor changes. The shape of hands and feet, length of limbs, the peculiar gait and demeanor are also important, as are also the slow pulse, slow respirations and subnormal temperature (see preceding section for details). In doubtful cases, the aid of the laboratory in diagnosis may now be invoked. Applicable tests are enumerated and criticized on page 683. Although we possess no absolute criterion for the determination of thyroid deficiency, yet the laboratory evidence of an endocrine and probably hypothyroid condition in the presence of symptoms suggestive of thyroid deficiency is of great diagnostic importance (Means and Aub, Plummer, Janney and Henderson). As the basal metabolism is more frequently and more deeply depressed in hypothyroidism than in any known condition, a determination of the basal metabolic rate should never be omitted, when possible to obtain the same in older children. Abnormalities in the differential blood count and blood-glucose curve are best regarded merely as general indications of endocrine disturbance. Roentgenologic studies are of importance in all doubtful cases (Siegert,[28] Hermann[20] and Hess[30]). This aid to diagnosis is frequently neglected.

In regard to the **differential diagnosis,** *true infantilism* (Falta) has been confused with hypothyroidism. The former condition is distinguished by a mere arrest of the development of the organism at an early stage. The psyche, skeleton and soft tissues are normal for an age younger than the age of the child suffering from infantilism. The pathologic changes of hypothyroidism are absent. *True dwarfism* is distinguished by a regular progressive symmetrical development of skeleton and soft parts, which do not reach the normal limits of adult size and stature. No cretinoid features are present.

Mongolism resembles hypothyroidism in its early onset and retardation of growth, stupid facial expression and protruding tongue. Mongoloids have a small round head, flattened posteriorly in distinction to the large brachycephalic head of the cretin. The Mongol's eyes have an Oriental slant; the nose, though small, is button-like, not retracted at the base showing flaring nostrils as does the cretin's. The tongue is small and pointed, the cretin's large, broad and tooth-marked. The neck is normal in length and the thyroid normal in size in Mongolism, but shortened and the thyroid small or not palpable in cretinism. The Mongol's hands are slender with tapered fingers and incurving little fingers, the terminal phalanx being displaced upon the short second phalanx, in distinction to the spade-like, plump, straight fingers and hands of the cretin. The bone nuclei and dentition changes are much less pronounced in the Mongoloid than in the cretin: Indeed, epiphyses may appear at the normal time in the former. The hair and skin change of the cretin are absent in the Mongol.

Congenital idiocy merely resembles cretinism in the mental sphere. The spasticity or paralysis of the limbs, disturbances of reflexes, etc., readily distinguish this condition. *Rickets*, in its typical form, does not resemble hypothyroidism. In doubtful cases roentgenologic studies will readily determine the specific hypertrophic, rachitic changes of the bones distinguished from the delayed ossification of the cretin's skeleton. *Chondrodystrophy* is a disease characterized by delayed development of the cartilaginous ossification centers resembling hypothyroidism only in dwarfism. No mental nor cretinoid changes in the soft parts are present. Typical chondrodystrophic dwarfs are too characteristic to permit of confusion. The Roentgen-ray will always clear up doubtful cases.

Relation of Hypothyroidism to Other Endocrinopathies.—Hypothyroidism may be associated either accidentally or as a part of a pluriglandular syndrome with diseases of other ductless glands. Mild signs of thyroid hypo-function are as a rule found in Fröhlich's Syndrome (bilobar hypopituitarism) according to many case studies by Engelbach, also in the writer's series. The hypothyroidism is probably secondary as it develops usually some years after the pituitary syndrome has established itself. Rarely, the two diseases may be superimposed from the start. Hypopituitarism is, however, not a sequela of cretinism. Two cases of hypothyroidism with acromegalic features have been observed in adolescents (Janney).

There seems no definite etiologic connection between hypothyroidism and mongolism, although changes have been detected at times in the thyroid glands of mongols. Rarely, mongolism and hypothyroidism have been clinically observed in association.

Treatment.—Medical treatment consists mainly in the administration of thyroid preparations. Some of the most brilliant results obtained in medicine follow their judicious administration. Growth begins anew, the myxedematous swellings disappear, mental and physical activity increase, and the child may gradually entirely regain its normal health and appearance. The results are by no means so perfect, however, as are indicated in most textbooks. Frequently growth remains somewhat retarded, even when the treatment is begun very early. Moreover, it is seldom that all signs of hypothyroidism entirely disappear. Three factors must be considered: (1) The amount of permanent structural change taken place previous to treatment; (2) the adequacy of the dosage; and (3) the activity of the thyroid preparations used. When, for example, epiphyseal closure has already taken place, treatment is much less effective as regards the osseous system. The writer has found a regular record of the dentition and serial roentgenologic plates, useful aids to treatment.

In severe cases thyroid preparations must be exhibited during the entire life of the individual. It is exceedingly important that the patient and relatives be sufficiently impressed with this necessity at the outset, as relapses from neglected treatment are frequent. On the other hand, certain mild cases appear to recover fully their growth and normal development, even when thyroid is no longer administered. In such cases, the thyroid gland apparently undergoes regeneration. There seems no reasonable excuse for giving thyroid preparations in doses sufficient to produce toxic symptoms, though this cannot always be avoided at the beginning of treatment. Various cases are reported in the literature where considerable harm has thus been done. A slight increase in pulse rate is, however, permissible at first. The writer is accustomed to decrease the dosage as soon as slight nervousness, tachycardia, or precordial oppression is complained of. In children normal growth is the result to be sought. A weight, height and dosage chart should be regularly kept. Overdosage will quickly prevent growth. This may be the only sign of the overdosage. It should be remembered that hypothyroid children may react with considerable toxicity to a minimal dose of thyroid at the outset of treatment, but later may bear larger doses without toxicity. A boy of seven years, exhibiting marked hypothyroidism, was given ¾ gr. of thyroid extract *per diem* and, after two days, reacted with rise of temperature to 104 degrees, flushed face, tremor, nausea and vomiting. Later this patient tolerated with benefit 2 gr. per day of the same preparation.

Effect on Metabolism.—During the past few years basal metabolic studies have been applied as control of the clinical treatment of hypo-

thyroidism in adults by Means and Aub, Plummer, Rowntree, Janney and others. The general conclusion is that the metabolic rate is the best-known control of thyroid therapy. In a few weeks at most the metabolic rate will rise to normal, the dose being then reduced and the patient observed at regular intervals in order to maintain the metabolism at normal by variations in the dosage. The writer for the past year has applied this method to all children old enough for observation with the small Benedict-Carpenter respiration apparatus. Results obtained have been most helpful and interesting.

There is said to be a preliminary loss of nitrogen due to the melting of the myxedematous tissues, but there is little experimental evidence for this. The studies of the writer have, on the contrary, shown that there is a nitrogen gain, not loss, on proper thyroid treatment, the nitrogen being probably used in the growth, replacement and repair of tissues.

Thyroid implantation, if successful, would be an ideal method of cure of thyroid deficiency. Unfortunately, no lasting results have been obtained by homeotransplantation, *i.e.*, thyroid gland transplantation from one animal to another of the same species, though autotransplantation has been experimentally successful. It seems that biochemical protoplasmic differences, even in individuals of the same species, are sufficient to cause ultimate absorption of the transplanted organ.

Preparations and Dosage.—There are at present a number of reliable commercial, dry thyroid extracts prepared. In view of present knowledge that iodin is a component part of thyroxin, the thyroid hormone, only those preparations are to be recommended which have a standardized iodin content. There is a tendency in the profession to give too great a dose at the beginning. Usually 2 to 4 gr. a day of the dried extract are sufficient in a pronounced case, and in the light cases, excellent therapeutic results may follow as little as ¼ or ⅛ gr. daily.

The same results are obtainable by thyroxin, which has recently been manufactured on a commercial scale. It is probable and desirable that the thyroid hormone in isolated form may come into general use to the exclusion of other preparations, particularly as much more exact results may be expected from its use. The daily dosage varies from 0.1 to 0.8 mg. tablets in usual cases. Thyroxin has been given intravenously with good results by Plummer and Kendall. Formerly iodin, locally or internally, thyroidin and other more or less impure or altered thyroid preparations were commonly used. Iodin is applied locally to reduce small goiters. As its therapeutic action most probably depends upon its absorption and conversion into thyroxin, the latter remedy should be as efficacious.

ENDEMIC THYROID DISEASES

The Cretinic Degeneration

Definition and Terminology.—A disease of endemic nature chiefly characterized by goiter, cretinism and deaf-mutism, occurring

singly or in association. The disease is conveyed by infected soil and water, and is caused by noxa, probably bacterial toxins, the exact nature of which has not yet been demonstrated. Though the thyroid chiefly is affected, the etiologic agents may act independently upon other tissues and organs producing a varying symptomatology, thus differing from sporadic hypothyroidism.

The term *Cretinic Degeneration* (Falta) is preferred to *Endemic Cretinism*, as being sufficiently generic to include the differing manifestations of the disease, many cases not being typical cretins, and some merely exhibiting thyroid hyperplasia, i.e., goiter, as the first reaction to injury of the thyroid by the toxic agent. As iodin is now known to be a component element in the thyroid hormone and even such simple adenomata are poorer in iodin than the normal thyroid, as well as being clinically the precursors of hypothyroidism in the individual or offspring, endemic goiter may be regarded as a symptom of thyroid deficiency and be included together with the other clinical manifestations (endemic cretinism, deaf-mutism and goiter heart) of a common etiology. *Endemic goiter* is not, therefore, treated as a separate disease in this work. One may be reminded, in this regard, that tuberculosis has likewise a very varied symptomatology, which, with increase of knowledge, underwent the same process of nosologic unification.

As the pathology and symptomatology of the cretinic degeneration in its typical form may be indistinguishable from sporadic hypothyroidism, according to the keenest students of the disease, in the succeeding pages space will be devoted only to the characteristic peculiarities of this interesting morbid condition. All the clinical forms (goiter, cretinism and deaf-mutism) will be considered as one disease, from endemologic, etiologic and pathologic standpoints.

Etiology of the Cretinic Degeneration.—Prevalence.—Though rare in its severe manifestation in America, the Cretinic Degeneration is one of the most common of all diseases. Important statistical data have been contributed by E. Bircher (Switzerland), v. Wagner, Baillarger (Australia), Lobenhoffer (France), McCarrison (India). In Switzerland, 7.2 per cent. of military applicants must be rejected for goiter. In France, 1873, 1 per cent. of the total population were goitrous, 0.3 per cent. cretins. In 1883, one of every 67 inhabitants in Piedmont, Lombardy, and Venice were goitrous or cretins. "In India, at the present time, not less than 5,000,000 persons are afflicted with goiter, while half a million is a low estimate of the numbers who suffer from its congenital manifestations" (McCarrison, 1917).

Cretinism, deaf-mutism and goiter heart are always much less common than endemic goiter, and occur in the children of goitrous individuals with great regularity. A mild epidemic is characterized by the development of many small goiters. As time goes on the severer forms of the disease appear. If the endemic retrogresses, cretinism and deaf-mutism tend first to disappear, the goiters then decreasing in size and frequency.

Statistics relative to occurrence in children are lacking, but the disease in goitrous districts is extremely prevalent in children. In some Himalayan villages, 60 per cent. of the young infants are goitrous. In America, Adami reports great frequency among the French-Canadians. Dock found an incidence of two to three per 1000 of all cases. The region of the Great Lakes, Washington, Oregon, California and Nevada show a high incidence of simple goiter (Osler,[31] Kerr,[32] etc.).

The common domestic animals, also fowls, pigeons, rats and mice, and fish may all be affected by goiter and growth anomalies suggesting cretinism. Animals and fish in captivity or in districts in which man is affected are much more likely to develop goiter. Congenital goiters and cretinism may occur in animals. Cretin lambs were very common at one time in Michigan. Goitrous and cretin white rats and goats have been born under experimenal conditions (McCarrison, etc.).

Geographical Distribution of the Cretinic Degeneration.—The disease is widely distributed, though some countries, for example the United States, may be comparatively free of it. The general recognition of its frequent presence in certain European countries is probably in part dependent upon the high development of medical science in such countries. Many more endemic areas are being discovered and reported as civilization progresses. The Cretinic Degeneration is found in all climates, though most often in the temperate and subtropical. Its frequent occurrence in mountainous districts has long been recognized. Such are the Alps, Pyrenees, Carpathians, Caucausus, Ural, Altai, Andes and Cordillera ranges. Certain English mountain valleys are also endemic localities. In view of the recent experimental production of goiter by fecal and filth contaminations of food and water supply (Marine, D., and Lenhart, C. H.,[33] also McCarrison) it seems likely that the unprotected water supply, the surface drainage and unsanitary conditions of mountainous districts to some extent account for the prevalence of the disease at high altitudes. McCarrison ingenuously suggests that the strain on the thyroid consequent to increased organic activity may be here a contributory factor. The plains are, however, by no means free of endemic goiter and cretinism, as they occur in Lombardy, Piedmont, Venice, Alsace and the river basins of the Lena, Obi, St. Lawrence, Ganges, Brahmaputra, etc. The seacoast is infrequently invaded. Possibly the iodin content of seawater and pelagic flora may tend to prevent its occurrence on coast littorals. An excellent monograph by McCarrison on the etiology of endemic cretinism contains a map showing geographical distribution.

Nature of the Soil.—Many efforts have been made to trace the noxa of endemic hypothyroidism to specific geologic formations (E. Bircher et al.). The practical point brought out in these studies has been the observation that the disease is more frequent in limestone formation. In view of recent studies, it seems much more likely that the adaptability, through porosity of the limestone rocks and limestone soil, to human habitation and to soil contamination is the factor of the

prevalence of goiter on certain geologic strata. This seems borne out by the common occurrence of cases in marshy regions along rivers and canals. Soil contamination by human or animal excreta has been demonstrated to be an important, perhaps the determining, cause of an outbreak of the disease (McCarrison).

Water Supply.—Closely connected with the matter of the soil and drainage is the matter of water supply. It has been long known that the noxa of endemic hypothyroidism may be transmitted by water. The examples of "goiter springs," brooks and wells quoted by the Swiss authors are well known to all readers on this subject. Families in good health moving into such areas supplied by goiter water become goitrous. Conversely the goiters may cease to grow, or grow smaller, should the family remove again to a healthier location. Communities become goiter-free on changing their water supply.

Season.—Epidemics of "summer goiters" occur. These seem related to the seasonal variation of the iodin content of the thyroid, which was shown by F. Fenger[34] in animals to be lower during March, April, May and June. During these months the gland is more liable to undergo hyperplasia, if the determining factors be present.

Heredity.—A hereditary tendency is undoubtedly present, inasmuch as affected parents, even on removal from goitrous localities, may in some cases have goitrous children. In endemic areas, however, both children and parents are exposed to the exciting cause of the disease. The fact that endemic cretins and deaf-mutes are usually the children of parents with goiters does not, therefore, prove hereditary origin. Probably both hereditary and subsequent exposure are etiologic factors in endemic areas.

Age.—Children, as compared to adults, are more frequently affected with goiter, and more frequently near or about puberty. Dimme found about 1 : 20 of all cases to be congenital. Congenital goiters are very frequent in badly affected areas. The age at which children are affected varies to some extent with the age and severity of the epidemic. In newly affected areas the goiters are met with at a more tender age. Later a resistance to the disease apparently develops. The goiters may then seldom appear before the eighth year.

Sex.—In small children, both sexes are said to be equally affected (McCarrison). At puberty, as in later life, the female cases predominate.

Predisposing Causes.—These factors have been excellently described by McCarrison, who, after calling attention to the rôle played by general infectious diseases, stated: "Amongst factors which impose an added strain upon the functional powers of the thyroid are residence at altitudes considerably above that of sea-level, defective air space, improper food or defective food-supply, puberty, sexual activity, menstruation, pregnancy and emotional states, such as fright and continued mental strain. Under all these circumstances, it is the accumulation of demand in the presence of the excitant of goiter which determines the enlargement of the thyroid gland. Amongst those

factors which favor the entry of the excitant or excitants of the disease into the body are unhygienic conditions of life, residence on damp soil, and an occupation or social status which involves close and continued contact with infected soil. It is for these reasons that goiter is much commoner amongst the laboring classes and in rural districts than amongst other classes of the community or residents in towns."

The Exciting Cause of the Cretinic Degeneration.—Every conceivable etiologic agent has been mentioned in the voluminous literature on this subject. Space does not permit a discussion of the various theories of the past. We may more profitably allude to certain prominent facts brought out by the older researches. The Cretinic Degeneration is unquestionably a place disease. One Swiss village may be badly affected; its neighbor escapes. The malady rarely develops in severe form under hygienic surroundings, such as modern cities or towns, but is nearly confined to rural districts. In these regions the infective agent has been repeatedly traced to the water supply and the incidence of the disease greatly reduced by introduction of pure water. The soil likely contains the infectious agent on account of the prevalence along rivers, in marshy areas, in the wet season of tropical countries and in mountainous districts where contamination of soil and water through the steep configuration of the land is common.

A purely metabolic or nutritional, etiologic hypothesis of the endemic hypothyroid is very unlikely, as healthy individuals without previous metabolic disturbance develop goiter in drinking "goitrigenous water" over a period of time and lose their symptoms to large extent on removal to a healthy location. A poor nutritional state is merely a contributory factor. By process of elimination we are then forced to seek for water-borne noxa which have either chemical or bacterial identity. In spite of active efforts and many analyses for the chemical hypothesis, no firm basis of support for a chemical theory has been discovered. Though more frequent in limestone waters, endemic cretinism is found in districts where soft water is present and again absent in other regions, in which the calcium content of the water is high. The assumption of "a specific colloidal poison" emanating from certain geologic formations is a purely speculative conception.

For the remaining possibility, a bacterial, etiologic agent, certain of the older data give considerable, later evidence almost conclusive, support. The significance of non-hygienic surroundings and localization of the disease to affected areas and the tracing of the noxa to the water supply have been mentioned. The fact that heating to 70°C. destroys the noxa was observed by Bircher, etc.

In 1906, McCarrison[35] pointed out the parallelism between the increasing incidence of goitrous individuals in seven villages on the Gilgit Fan, a river in India, and the increasing impurity of the river water, as it descended. This observation was strikingly corroborated in experiments by Marine and Lenhart,[33] also Gaylord, 1909 to 1912, in studying goiters of artificially bred trout. In such fish confined in

tanks, one above the other, a progressive increase was observed in thyroid hyperplasias and actual goiters of fish in the lower tanks. Iodin, pure water, addition of mercuric chlorid or arsenic to the tanks, or removal of the affected fish to their normal surroundings, caused the hyperplasia to grow less or disappear. Scrapings from the side walls of affected tanks produced goiters in healthy trout.

McCarrison's further studies on the epidemicity and etiology of goiter, as collected in his recent monograph (see bibliography), have been protracted, exhaustive and important in results. Perhaps the slowness of recognition of this work by American and English authors is due to its being carried out and largely published in India. This worker showed in 1910 that the residue left on a Berkefeld bacterial filter by goitrigenous water was capable of producing goiter in man. Gaylord (1912) demonstrated the same for cats and dogs. McCarrison, later Sazaki, showed that water contaminated by feces from goitrous human individuals, when consumed by goats, produced goiter in such goats. White rats showed similar positive results. The incidence of goiter among children was reduced 50 per cent. by the substitution of a pure water supply for one showing fecal contamination by bacteriologic control. White rats eating food contaminated by their own feces or fed on anaërobic fecal cultures from goitrous persons showed goiters after six months, in 100 per cent. of cases. The goiters in the later cases showed marked fibrotic changes. The most striking results upon the offspring of goats were obtained by feeding cultures of fecal bacteria secured from goitrous persons. After the goats became goitrous, they were impregnated. Of 11 kids born, 10 were stillborn. All had large goiters. The 10 stillborn were hairless, macerated and ill-developed cretins. The experiments were carefully controlled. Similar studies with white rats also yielded cretins and goitrous offspring. Vaccines prepared from intestinal organisms and intestinal antiseptics caused human goiters to diminish in size. This observation was confirmed by Messerli.

McCarrison concludes from his researches that the Cretinic Degeneration is caused by intestinal toxemia of bacteriologic origin in conjunction with the pre-disposing factors as mentioned. The anaërobic types of fecal bacteria are regarded as especially active in producing the disease. It is difficult not to accept as conclusive his carefully planned and controlled studies. They are also particularly important in bringing out experimentally the etiologic identity of cretinism and congenital goiter arising in offspring of goitrous individuals and serve to link these various manifestations to one common exciting cause. Should these experiments be fully confirmed by other competent observers, the etiology of the Cretinic Degeneration may be regarded as established as a bacterial toxemia. It is evident that the bacteria themselves are not directly responsible, as goiters have long been known to be sterile.

Pathologic and Clinical Characteristics of the Cretinic Degeneration.—If we accept endemic hypothyroidism to be a

disease dependent upon intestinal toxemia affecting the thyroid, we must then admit of two etiologic factors: *viz.*, the primary toxemia, affecting the organism generally and, secondarily, its local effect upon the thyroid gland and the consequent development of hypothyroid symptoms. We thus arrive on the basis of new experimental data to the older "dualistic" viewpoint as supported by H. and E. Bircher, Pineles, Ewald, E. Wieland, Falta and others who, as opposed to the "Unitarians," Kocher, Hertoghe, Siegert, etc., are unable to reconcile certain irregular clinic and pathologic manifestations in the picture often presented by cretinic degeneration with those of sporadic hypothyroidism. Some of these clinical differences may possibly be due to the toxic agents of cretinic degeneration affecting ductless glands other than the thyroid. The frequent observation of goitrous degeneration of the hypophysis in endemic cases would thus be accounted for. Possibly a certain group may later be differentiated on a pluriglandular basis (Schönemann).

As already emphasized there may be, however, no demonstrable difference between the pathologic and clinical aspects of the cretinic degeneration and sporadic hypothyroidism, except the endemicity of the former. Differences are therefore only alluded to in this section. The endemic cases develop, as a rule, at a later age than the sporadic, a period of exposure to the causative factors being apparently required. The skeletal changes are disproportionate and irregular, and are usually slighter. The bones may be heavy and are slightly bent or straight and gracile.

The greatest retardation of growth usually takes place in the second decenium (E. Bircher). Clinically one is impressed by the predominance of certain symptoms, such as goiter idiocy and deaf-mutism. It seems possible that the toxemia probably responsible for the thyroid injury may directly attack the central nervous system and cranial nerves, and that the greater frequency of idiocy and deaf-mutism may be relegated to this cause, as well as to thyroid deficiency. There is, in many cases, a prominence of the nervous and mental symptoms, the signs of hypothyroidism remaining in the background. Certain cases may, however, show marked goitrous degeneration of the thyroid and growth retardation, the mentality being little affected.

Nervous Cretinism.—This type of endemic cretinism is described by McCarrison, who found one-third of all Himalayan cretins to belong to this category. The same syndrome has also been reported in England. McCarrison defines nervous cretinism as "cretinous idiocy with associated diplegia and tetany due to congenital fibrosis of the thyroid and parathyroid glands." There is usually an accompanying deaf-mutism. Such children exhibit typical tetany and are frequently too spastic in the lower limbs to permit their standing. On autopsy of one case, great increase of fibrous tissue was found in the thyroid and absent para-thyroids on careful search. Further pathologic and clinic studies of this interesting syndrome are highly desirable.

Endemic Deaf-mutism.—Pathologic studies of this grave and frequent expression of the cretinic degeneration have led to the finding of developmental deficiencies in the cochlea and middle ear. Myxedematous thickening of the tympanum, etc., have also been regarded as causes of the deafness. According, however, to Pineles' studies, developmental and degenerative defects of the cortical centers are probably chiefly responsible. When hearing is absent in young cretins, speech is inhibited, just as in deafness from other cause. There is, however, no fixed relationship between the disturbance of hearing and speech, for the hearing may be excellent, while intelligence and speech are poorly developed. On the other hand, endemic cretins with high mentality may be quite deaf. Probably cortical lesions as well as peripheral defects in the organs of speech play a rôle. The hoarse or raucous voice of the cretin is due to myxedematous thickenings and perhaps also to muscular weakness of the vocal chords.

Other differences in the clinic picture of the cretinic degeneration as compared to sporadic cretinism may be noted. The myxedematous swellings are less frequent. The face may be pinched, chalky-white, or pigmented. The effect of thyroid therapy is not nearly so certain as in hypothyroidism of non-endemic origin. Some cases of idiocy and deaf-mutism may show little response to the same. It is likely, however, that, with the control of thyroid treatment by modern basal metabolism studies, better results may be expected.

The **differential diagnosis** of the cretinic degeneration from sporadic cretinism is inconsequential, as the two conditions may be, as noted, indistinguishable. Attempts at differentiation, made by certain German authors, seem but to emphasize this. The endemicity, frequency of goiter, deaf-mutism and goiter heart are chief characteristics. For other diseases which may lead to a mistaken diagnosis, see section on "Hypothyroidism."

The metabolism of the cretinic degeneration has rarely been the subject of research. It is, however, likely that in typical cases no striking differences will be elicited between endemic and sporadic hypothyroidism, as exemplified by Scholz's studies,[36] the only available, but these are rendered of somewhat dubious value through the inaccurate methods of analyses then employed. They show, however, a reduction of the urinary volume and of the exchange of protein, uric acid, creatinine and sodium chlorid. It is indeed highly desirable that a clinical study of cretinic degeneration with the aid of basal metabolic rate determinations be made in endemic areas on a large scale.

Goiter Heart.—The common occurrence of cardiac deficiency among goitrous subjects, accompanied or not by murmurs and hypertrophy, has long been known. Although less often observed in children than adults, Schranz found, on investigation of large material by autopsy, 23 per cent. of goitrous children to have cardiac disease characterized by myocardial degeneration, and at times hypertrophy. We have here an example of the widespread organic changes induced by thyroid deficiency, although we cannot exclude in endemic cretinism

the possibility of a direct toxic action on the cardiac muscle by the causative agents in that condition (Bircher, Minnich). Hypertrophy and dilatation of the right heart may be caused by the pressure of a large goiter (Rose) which may lead to respiratory embarrassment (Kocher's pneumonic goiter heart). Myocardial degeneration is also found in severe thyrotoxicosis. Goiter heart may be more properly regarded as a symptom of thyroid disease, rather than a morbid entity.

Treatment of the Cretinic Degeneration.—Hygienic Treatment.—In view of recent studies this has become of considerable importance. Every effort to prevent soil and water infection should be carried out. A pure water supply protected from surface drainage and, if possible, controlled bacteriologically should be the first criterion. Fecal disposal is of prime importance. A thorough renovation of dwellings or removal to an uninfected locality may be advisable. An educational hygienic campaign in endemic areas should, in view of the spread of the disease among the very poor, be an excellent adjunct to treatment. A plentiful well-balanced mixed diet is indicated. Suitable dietetic restrictions must be employed when intestinal stasis or colitis are present.

Medical treatment consists mainly in administration of thyroid preparations. For details see section, "Treatment of Hypothyroidism." As is known, certain cases of endemic cretinism do not respond very favorably to this form of medication. This is probably due to their symptoms resulting in part from a general toxemia of intestinal origin. Excellent results of treatment directed to the gastro-intestinal tract have been reported by McCarrison and Messerli. Thymol in 10 gr. doses, excluding from the diet its solvents, is recommended as disagreeable but effective. Salol, *B*-napthol, dilute hydrofluoric acid (1: 500) in doses, minims 20 to 40, also bacilli bulgaricus milk are recommended. Autogenous vaccines made from intestinal cultures or staphyloccous vaccines have, in the usual doses, caused endemic goiters to disappear in certain instances. Endemic deaf-mutism and idiocy are more resistant to treatment. Certain cases are resistant to any known form of therapy and may become public charges.

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CHAPTER LXXXIII

DISEASES OF THE PARATHYROID OR BRANCHIAL GLANDS

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Historical.—Knowledge of the existence of the parathyroid bodies is comparatively recent. They were discovered in 1880 by Sandström,[1] the Swedish anatomist, who, misled by the close association of these glands with the thyroid, regarded them as embryonic thyroid tissue. Sandström failed to contribute to an understanding of parathyroid physiology. Gley,[2] however, in 1891 took up the study of the function of the parathyroids and tetany but was unable to distinguish between the action of the thyroid and parathyroid upon the organism. Gley's work, however, served to stimulate a number of important studies which followed shortly afterward.

The embryologic and anatomic studies of Prenant and of Kohn, a few years later, determined the independence of the parathyroids from the thyroid gland. The careful researches of MacCallum,[3] Vassale and Generali,[4] Erdheim,[5] Biedl,[6] and Welsh[7] finally made it evident that tetany was caused by failure or loss of parathyroid function and that hypothyroidism was due solely to injury or lesion in the thyroid gland.

The clinical syndrome of tetany was first described by Clarke,[8] 1815, Cheyne,[9] 1819, and Steinheim[10] in 1830. Corvisart later suggested the appelation "tetany."

An excellent review of the historical development of this subject is that of v. Frankl-Hochwart[11] in Nothnagel's System of Medicine to which reference may be made for a detailed presentation.

Nomenclature.—It is unfortunate that the original confusion of parathyroid with thyroid function has been augmented by the adoption of the term "Parathyroid glands," Eng.; "Glandules parathyroidiennes," Fr.; "Ghiandolæ paratiroidee," Ital.; "Nebenschildrüsen," Ger. In the literature of the latter country, these organs are frequently designated "epithelial bodies" (Kohn), which is also open to criticism. The term "parathyroid" has, however, been made far too current by usage to be readily replaced by a better. In this regard, the writer is, however, inclined to follow the suggestion of Dock to employ Verdun's excellent term "*branchial glands*" as a synonym in the hope that it may gradually find its way into the literature. The term "hypoparathyroidism" or "branchial gland deficiency" is preferred to "tetany" or "spasmophilia" for etiologic reasons men-

tioned under that subject. "Spasmophilic diathesis" (Heubner) is synonymous with tetany.

Embryology, Anatomy, Histology.—The parathyroids begin their development as paired, endothelial thickenings of the third and fourth branchial arches (hence, the term "Branchial Glands"). The primary cell collections become solid cell masses separating themselves from the primitive gill clefts. The third arch pair wanders downward becoming the inferior parathyroids, while the glands springing from the fourth arch become the upper pair (Hertwig). The descent of the parathyroids accompanies that of the thyroid.

In newborn babies the color of these branchial glands is almost transparent. Later, they acquire a clear brown color, differing thus, as well as by their softer consistency, from the more dense thyroid tissue or neighboring lymph-nodes (MacCallum). In shape, the parathyroids are elongated, flattened, elliptical. One pole may be thicker than the other. The average weight of each adult human gland is, according to Vincent,[12] 0.035 gm., therefore even less in children. In man the number of these glands is usually four, arranged in superior and inferior pairs. Considerable variation may, however, occur. According to Strada's[13] recent report of 168 cases examined by him, four glands were present in 86; less than four in 76; more than four in 10; three in 7 cases; two in 5 cases.

The location of the upper glands is always alongside the trachea, usually in relation to the posterior surfaces of the lateral trachea lobes. The lower glands usually lie against the lower third of the posterior aspect of the thyroid lobes (Pool) but may migrate as low as the thymus (Falta) or even be found in relation to the pericardium (Vassale and Piana). The parathyroids are richly supplied by the blood from their arteries, branches of the inferior thyroids.

As to *structure*, each gland is surrounded by fibrous capsule strands which support the stroma cells. In early childhood they present on section a peculiarly homogeneous appearance. The slightly lobulated appearance of the adult gland has not yet become differentiated. The cells are large, sharply marked off, of polyhedral contour with palely staining protoplasm. The heavily staining *oxiphile cells* only occur, according to Welsh[14] who first described them, late in childhood and not before the tenth year. Others, however, have found these elements, even in the earliest years. The *fat cells* described by Benjamins and Erdheim are rarely met with in the very first years of childhood and likewise become increasingly frequent as age advances. *Glycogen* is present in especially large amounts in childhood (Guizetti). *Colloid cysts* are also present and are said also to gradually increase in number with age. The endocrine nature of the parathyroids is shown by the presence of a rich capillary network, the endothelial terminations of which are in closest contact and the secretory cells.

Function of the Parathyroid Glands.—**Experimental parathyroidectomy** is followed by a latent period with usually excellent surgical recovery. A few days later the musculature of the

animal becomes spastic and fibrillary contractions of the tongue and other muscles, especially on mechanical stimulus, are observed. The animal soon becomes unable to walk. During this period of tetanic convulsions the body temperature, respirations and pulse rate may be high. The special clinical symptoms of tetany (see below), including galvanic and sympathetic irritability, are present. All parts of the vasomotor mechanism, sympathetic cells, neuro-muscular nerve endings and musculature are affected (Hoskins and Wheeler).[15] A period of depression characterized by the absence of convulsions may then ensue alternating with succeeding convulsions and depressive periods terminating in coma and death of the subject a few days later.

The Metabolism of Hypoparathyroidism.—Fundamental changes in the metabolism after parathyroidectomy have been reported from many sources. The metabolic findings following experimental thyroidectomy have been summarized by Voegtlin[16] in the following table.

METABOLIC CHANGES FOLLOWING PARATHYROIDECTOMY IN DOGS (VOEGTLIN)

	Pretetany stage	Active tetany
Total nitrogen metabolism	Normal	Increased
Urinary ammonia	Normal	Increased
Blood ammonia	Normal	Increased
Urinary creatinine	Normal	Increased
Urinary creatine	Normal	Increased
Urinary phosphates	Decreased	Increased
Blood phosphorus	Decreased	
Urinary sulphates and neutral sulphur	Normal	Increased
Urinary rest nitrogen	Normal	Increased
Urinary toxic bases	.....	Present
Urinary lactic acid	Absent	Present
Urinary Ca and Mg	Increased	Increased
Blood calcium	.....	Decreased

The detoxication theory of parathyroid function has recently received an added impetus through L. R. Dragstedt's important experiments. This worker in animal and therapeutic experiments demonstrated that tetany could be cured in parathyroidectomized dogs by a high carbohydrate diet and life indefinitely prolonged. When meat was fed tetany soon intervened the animal succumbing. The protection from tetany due to carbohydrate feeding is explained by the ensuing change of flora preventing protein putrefaction and toxic amin formation (Kendall, A. I.). Thus, these researches are linked to those of Noel Paton and co-workers, relative to the sig-

nificance of guanidin tetany. Dragstedt's conclusions may be quoted as follows:

"1. Parathyroid tetany or depression is due to an intoxication.

"2. The responsible toxic substances come chiefly from the gastrointestinal tract. They arise through the activity of the proteolytic group of intestinal bacteria, and are probably for the most part protein split products of the nature of amins.

"3. The function of the parathyroid glands is to prevent intoxication by these poisons.

"4. The parathyroid glands do not furnish a hormone necessary for life, and dogs may be kept alive indefinitely after their removal, if treatment directed to the prevention of this toxemia of intestinal origin is carried out."

The relation of the parathyroids to the *mineral metabolism*, particularly that of the *calcium*, has been the subject of intensive investigation. This grew out of data of the influence of calcium salts on nervous tissue which had previously been acquired. *Sabbatani*[17] observed that application of calcium salts to the cerebral cortex lowered their excitability. This observation checked with that of Loeb[18] who showed that substances precipitating calcium heightened nervous irritability. Quest[19] observed the high cerebral calcium content of the newborn and thus accounted for the low nervous irritability of such infants. The reduction in amount of this element in the brain of older children corresponds to their proneness to convulsive seizures. MacCallum and Voegtlin,[20] who have carefully studied the relation of calcium to tetany, found the brains and blood of parathyroidectomized dogs poor in calcium, which was eliminated in increased quantities in urine and feces. Numerous other investigators have corroborated these findings. Later, MacCallum, Lambert, and Vogel[21] found that calcium-free blood or blood from a dog with tetany perfused through the leg from a normal dog produced muscular irritability, and *vice versa* normal blood perfused through the leg of a tetanized dog decreased the irritability. It was soon discovered that tetanic convulsions in the human being are controlled by calcium administration (MacCallum and Voegtlin,[22] Howland and Marriott,[23] Netter,[24] Göppert[25]). Also it is now known that hypothyroid extract can cause a retention of calcium and magnesium (Freund and Lockwood[26]).

The close relationship of the calcium metabolism to the parathyroids has been emphasized by the researches of Erdheim,[27] Hohlbaum,[28] Iselin,[29] Morel,[30] Toyofuku[31] who observed the appearance of enamel defects in the teeth of parathyroidectomized rats, also delayed ossification and union of fractures. Boez[32] reported stimulation of ossification by dried parathyroid extract.

Parathyroid metabolism is, however, much more complicated than the above facts would indicate. It was later discovered that other inorganic salts, magnesium, strontium (Voegtlin),[33] also phosphate solutions (Binger),[34] relieve the symptoms of tetany temporarily precisely as does calcium. D. W. Wilson, T. Stearns, J. H. Janney, Jr.,

and M. DeG. Thurlow[35, 36, 37] in a series of recent articles discovered that acids, namely hydrochloric acid, prevented and relieved tetany. These investigators showed that a state of *alkalosis* develops after parathyroidectomy. "There is a marked diminution in the excretion of acids and ammonia, accompanied by a decrease in the ratio in ammonia-nitrogen to total nitrogen and in the hydrogen-ion concentration of the urine. After the development of tetany, the excretion of acids and ammonia increases as well as the ammonia-nitrogen ratio and the hydrogen-ion concentration of the urine." In the pretetanic alkalosis state there is then a relative increase of fixed alkalie as this is the significance of lowered ammonia-nitrogen content of the urine according to a former investigation of the present writer.[38] The increase of alkalie in the hypoparathyroid condition would also explain the occurrence of tetany after sodium bicarbonate administration (Howland and Marriott,[39] also Harrop[40]). Togawa[41] has recently essentially corroborated the studies of Wilson and co-workers on the acid alkalie balance in tetany. The similar, but apparently unrelated therapeutic effect of both acids, calcium and other salts in relieving tetany is explained by these investigators in finding that such agents both lower the value of the dissociation constant of oxyhemoglobin and alveolar carbon-dioxide pressure. This work is of fundamental importance in explaining the metabolic changes occurring after parathyroidectomy and as a result of tetany.

In common with the ductless glands the parathyroids exercise an influence on *carbohydrate metabolism.* In spite of much contradictory evidence due to the confusion of thyroid with parathyroid function, it is now recognized that the assimilation limits for glucose are lowered by parathyroidectomy (Eppinger, Falta, Rudinger,[42] *et al.*). In spite, however, of this observation, hypoglycemia is usually reported in tetany (Watanabe,[43] Underhill and Blatherwick[44]). Calcium administration causes the blood glucose to return to normal limits but this seems an indirect action.

Noel Paton and his co-workers in recent years have very thoroughly studied the relation of *guanidin* to tetany. Burns and Sharpe[45] found a marked increase in the guanidin content of the blood after experimental parathyroidectomy as well as in the urine of children suffering from idiopathic tetany. Guanidin was found to produce tetany having the same metabolic characteristics as the tetany of parathyroidectomy (Burns[46]). Watanabe's[43] subsequent studies demonstrated an acidosis, phosphate retention and hypoglycemia, and decrease of calcium metabolism in guanidin tetany which findings showed a further agreement with the usual forms of tetany. It was concluded that the parathyroids regulate the metabolism of guanidin in the body and thus control muscle tonus. Tetany is therefore regarded as a toxic manifestation due to the accumulation of guanidin whether through removal or through disease of the parathyroid (Burns and Watson[47]).

It is well at present to adopt an extremely conservative attitude in regard to the metabolism of tetany. Many facts are still contradictory

and apparently unrelated. One had best await the gathering and recording of more exact experimental data without attempting a premature correlation of the same.

The **relation of parathyroid to thyroid function** has been the matter of considerable confusion, resulting evidently from the close anatomic relationship of these two endocrine organs with attendant obstacles in experimental work. A further source of difficulty has been a tendency to extend the hypothesis of close interrelationship of the endocrine glands of the Vienna school to include the parathyroids. To go into the intricate theoretical questions here involved would be a too lengthy consideration for the present article. Suffice it to state that no precise or definite collaboration or antagonism has been established between the parathyroids and thyroid or indeed any other endocrine gland. It is, however, probable that the cellular nutrition and metabolism of each endocrine organ is to some extent controlled by others, which accounts for the hypertrophic or atrophic processes in other glands following the functional insufficiency or removal of one member of the endocrine system. Thus Tanberg[48] in an excellent article noted the failure after parathyroidectomy of the usual hypertrophy of the thyroid following ingestion of meat and a tendency to thyroid atrophy, clearly states the accepted modern view, as follows.

"The parathyroids and thyroids are independent organs, each having specific functions. This, however, does not exclude the occurrence of a direct or indirect interaction in the functions of the two systems.

"There is reason to believe that an insufficiency of the parathyroid gland checks to some extent the function of the thyroid gland. No proof of the existence of a vicarious coöperation between the two glands has been established."

HYPOPARATHYROIDISM: BRANCHIAL GLAND DEFICIENCY

Definition.—An endocrine deficiency disease due to decreased parathyroid function and characterized by certain trophic phenomena, heightened excitability of the nervous system and tetany.

In the past, too much emphasis has been given to the phenomenon of tetany or spasmophilia without due appreciation that the same is but a striking clinical symptom. Exception is taken, therefore, to regarding tetany as a definite nosologic entity. It is much safer and avoids confusion to look upon it rather as a symptom-complex arising from a heightened nervous irritability, especially characteristic of, but by no means limited to, a condition of deficiency of the parathyroid glands. With the aid of this viewpoint, it becomes thus unnecessary to endeavor to include under this glandular deficiency disease every form of tetany, the propriety of which is becoming very doubtful. Thus Binger[34] has been able to produce typical tetany in dogs with intact parathyroids.

Etiology.—Although hypoparathyroidism or branchial gland deficiency must be regarded as always due to functional deficiency of

these endocrine organs, lesions in these glands have, however, not been found in all cases. This, however, does not necessarily militate against acceptance of a functionally imperfect gland without demonstrable pathology. The regular appearance of tetany and other clinical signs of hypoparathyroidism after extirpation of these minute organs together with the appearance of practically identical metabolic and trophic changes in parathyroidectomized animals and human subjects of so-called "idiopathic tetany" make it very probable that these conditions are one and the same condition. The connecting link between experimental and idiopathic tetany is post-operative tetany in which Erdheim and others demonstrated that the parathyroids had been removed with the thyroid gland in goiter operations.

Hypoparathyroidism is more common in northern countries. Seasonal variation is considerable. The disease is especially prevalent in the first months of the year, particularly in February, March and April (v. Frankl-Hochwart,[11] Thiemich,[49] A. Brown and A. Fletcher.[50] Increased incidence in the spring months occurs both in adult and children's cases. Thiemich,[51] McCarrison[52] *et al.* emphasize the hereditary and familial tendency of hypoparathyroidism. Children of mothers developing the tetany of pregnancy are especially prone to the disease. Pool[53] quotes Peter's observation of death by convulsions of 9 of 10 children of a woman suffering from tetany in each pregnancy, except the first. McCarrison mentions the frequency of the association of tetany and hypothyroidism.

The age of pre-disposition to hypoparathyroidism is from the fourth month to the end of the third year, although cases occur in later childhood.

In certain localities, hypoparathyroidism may become so frequent that "epidemics of tetany" are spoken of.

Unhygienic surroundings as an etiologic factor are mentioned by Pineles, *et al.*

Hypoparathyroidism occurs in typhus and cholera epidemics (Pineles), also associated with helminthiasis, rheumatism, malaria and other infectious diseases. The close association of tetany with diseases of the intestinal tract has long been remarked but it is not certain that parathyroid deficiency is present under these conditions.

Kassowitz and his colleagues believe tetany to be but a symptom of rickets. Although these conditions are frequently associated, yet typical rickets is often present without tetany and *vice versa*. Schmorl[54] failed to find parathyroid lesions in rickets. Howland and Marriott have recently missed the characteristic tetanoid lowering of the calcium content of the blood in rickets, thus supplying metabolic evidence against the identity of the two conditions.

Attempts to relegate hypoparathyroidism to dietary etiologic factors have not been very convincing. Finkelstein believed whey of cow's milk to be causative.

Tetany is more common in artificially fed than in breast fed children but the exact reason is not obvious. Efforts to trace it to vita-

min deficiency have been unavailing. A. Brown and A. Fletcher have recently advanced the interesting view that tetany is produced by foods high in carbohydrate heated to the boiling point.

The relation of calcium and guanidin to the etiology of branchial gland deficiency has been alluded to in a previous section. Paton and co-workers regard guanidin intoxication as the chief etiologic factor but fail thus to account for the trophic disturbances of hypoparathyroidism which accompany tetany in the human being. Calcium deficiency also has failed to prove a direct etiologic factor in production of the disease, as calcium therapy merely controls the convulsion but is not curative.

Like the thyroid and other ductless glands, the parathyroid has been thought by some to function in the removal of toxins from the blood which on injury to this endocrine organ by disease or trauma multiply and cause the symptoms. This detoxication theory still remains an ingenious but unproven hypothesis. Compare Falta's[55] able discussion of this point.

In tetany of the newborn, birth traumatism may be a causative factor inasmuch as parathyroid hemorrhages may be so induced, but it is difficult to thus explain the great frequency of the disease after the fourth month and the relative infrequency in the newborn.

Pathology.—There is little exact knowledge of the pathology of hypoparathyroidism. A number of lesions have indeed been described in the parathyroids but it is uncertain whether such lesions are the cause or even indirect cause of the symptomatology in all cases. Thus Guizetti[56] has reported in a fatal case of traumatic tetany (an eight year old child) edema of the parathyroid. Thompson,[57] on the other hand, found no pathologic change in these glands or other organs in a case aged 11 years dead of the same cause.

The most frequent and characteristic pathologic feature of the parathyroids is the presence of *hemorrhages*. Erdheim[58] was the first to describe such in cases of tetany in children. The fresh blood extravasations tend later to become encapsulated by radically disposed epithelial cells. Yanase[59] in Escherich's clinic *et al.* have described the presence of blood collections in many cases of tetany in infants and children. Auerbach,[60] Grosser[61] and others have, however, found hemorrhages in many infants without tetany, also noted no constant pathologic changes and the absence of hemorrhages in tetany cases. It is likely, however, that certain cases of tetany are due to parathyroid hemorrhages incurred by birth, which according to Haberfeld[62] may lead to hypoplasia of these organs.

Other pathologic lesions such as areas of supposed chronic inflammation (Gezowa[63]) and cyst formation have been reported without knowledge of causal relation to tetany.

Of the pathologic lesions in the nervous system, somatic organs and musculature, there is but fragmentary knowledge. Changes in the skin and its appendages will be alluded to in the next section. Schüller,[64] Falta have reported cases of recurring tetany with retarda-

tion of ossification. The same has been noted after experimental parathyroidectomy. A definite relationship between juvenile osteomalacia and parathyroid deficiency has not been certainly demonstrated.

Symptomatology of Hypoparathyroidism in Children.—There is no essential difference between the tetany of children and adults, and has been thoroughly emphasized by Pineles.[65] It is beginning to be recognized that decrease in or loss of parathyroid function not only affects the nervous system alone but also the tissues and organs generally. This would likewise seem very likely upon *a-priori* grounds in view of our present knowledge of the far-reaching effects of other endocrine glands upon the organism. As would be expected in the case of an organ indispensable for the continuance of life, a *chronic cachexia* and *trophic disturbances* are quite common, though frequently overlooked on account of attention being focused upon the very striking nervous phenomena characteristic of the disease. The *retardation* of *development* is emphasized by v. Frankl-Hochwart, Escherich, Thiemich, Falta. Schüller's observation of the presence of delayed bone formation, rarefaction on the trabeculæ and osseous atrophy, included three juvenile cases of occupational tetany. The close association between hypoparathyroidism and rickets has been dwelt upon by various writers, recently by Bitter[66] and Fromme.[67] Escherich[68] states that tetany in children is associated with rickets in 80 to 90 per cent. of cases. As already pointed out, the weight of evidence lies against any direct causal relationship.

Changes in the skin and subcutaneous tissues and its appendages are not uncommon. Puffiness of the face, localized swelling of the extremities may be present and due to angiospasm (v. Frankl-Hochwart). Pallor is usual but flushing at small provocation occurs due to the vasomotor instability. Abnormal pigmentation is rare. Thinning and splitting and loss of hair is reported (Hoffman,[69] etc.), which may grow worse before a tetanic outbreak. The nails may become thin, seamed or brittle but, contrary to the rule in adults, entire loss of the finger nails is very rare in children. Disturbances in dentition are common; enamel defects especially frequent (Fleischmann,[70] *et al.*). This would be expected from the regulation of calcium metabolism exerted by the parathyroids.

The **musculature** may be undeveloped and weak as a part of the general cachexia. Myotonia may be present.

Cardiovascular System.—The heart may exhibit tachycardia and increased muscular contractability in tetany. Sudden death in infantile tetany not due to spasm of glottis has been ascribed by Ibrahim[71] to cardiac failure through vagus or sympathetic irritability.

The blood is characterized by polyglobulia which according to Falta exists only in the acute stage and is due to leukocytosis. The polymorphonuclear cells may be decreased and the lymphocytes and eosinophiles augmented in numbers (W. Haas[72]). The leukocyte formula is thus similar to that found in other endocrine deficiency

diseases. These statements chiefly refer to adults, as blood studies in hypoparathyroid children have not been made *in extenso*.

The Gastro-intestinal Tract.—A number of chronic gastro-intestinal conditions such as gastric or intestinal dilatation, stagnation and auto-intoxication are characterized by tetanic outbreaks, *gastric tetany*. There is, however, no existing proofs that in such cases a true functional deficiency of the parathyroid is the causal factor present (see "Etiology"). Mention is therefore made here only of those conditions which may occur as an accompaniment of tetanic attacks where loss of parathyroid function can be accepted. In this case, pylorospasm, hypersecretion and dilatation of the stomach may occur (Falta and Kahn,[73] Ibrahim[71]). The latter describes in suckling infants spasms of the sphincter and with great gaseous distention of abdomen. Evidence of increased intestinal tonus leading to diarrhea may be present.

The genito-urinary system may be affected. Retention of urine due to vesical spasm occurs in young infants (Ibrahim, Escherich, *et al.*). Busco[74] has recently attributed enuresis in infants with motor hyperexcitability to parathyroid deficiency. A. Brown and A. Fletcher[50] in an interesting article call attention to a certain relationship observed by them and others between the occurrence of sodium chlorid retention edema and tetany in children which subsides on relief of the edema. Parathyroid deficiency has no very appreciable effect upon the genital organs so far as their development in childhood is concerned.

The Nervous System.—The chief clinical symptom of hypoparathyroidism is the *tetanic convulsion* or *tetany*. Allusion has already been made to the confusion caused by regarding this symptom-complex as a disease *per se*. Though characteristically frequent in parathyroid deficiency, it also occurs in certain gastro-intestinal conditions such as acute auto-intoxication in children. In the present treatise therefore tetany is described and treated merely as a clinical syndrome characteristic of but not confined to parathyroid deficiency. See the excellent article of Howland and Marriott for objections to regarding hypoparathyroidism as the cause of infantile tetany.

Tetany manifests itself as tonic convulsions of the extremities. The upper are most often affected. The convulsions are usually bilateral but "hemitetany" is rarely met with (v. Frankl-Hochwart, v. Jaksch, H. and E. Freund, *et al.*). The forearms are flexed on upper arms, the hand upon the wrists, the fingers, however, extended and approximated in the classical "obstetrical" position. The upper extremities may thus show the characteristic gesture of a pet dog begging. The feet are less often affected. They assume the *pes varus* or *equino-varus* and *cavus* positions. The toes may, however, be extended. In a severe attack the head and trunk may become affected. The expression becomes rigid and the mouth contorts itself into a snout-like or carp-like appearance. Fibrillary muscle contractions and true epileptiform convulsions may occasionally be noted. Laryngospasm is common in children. Among rare symptoms are dyspnea

from tonic contraction of the respiratory muscles and diaphragm, retching spasms, pupillary rigidity, difficulty of deglutition, retention of urine. The spasms may be very painful which adds to the miserable state of tetanic children.

"Latent" tetany, *i.e.*, a state of motor hyperirritability between the tetanic convulsion, may be detected by use of special diagnostic methods, as follows:

Trousseau's phenomenon consists in the production of a tetanic convulsion of the hand by pressure on the nerve trunks in the internal bicipital groove. Sufficient force to produce cyanosis must be employed and be continued for several minutes in order to bring out the effect. This sign, as it occurs in no other condition, is pathognomonic of tetany when present. Trousseau's phenomenon may, however, be absent in typical tetany.

Chvostek's or the Facial Phenomenon consists in contractions of the facial muscles elicited by tapping over the course of the facial nerve in the cheek midway between the zygomatic process and the angle of the jaw. In severe cases gentle stroking may cause such contractions (Schulze's phenomenon). There is much difference of opinion as to the value of this sign. By the older authors, it was regarded as invariably indicative of tetany. J. Howland and W. McK. Marriott[23] believe that the age factor is of much importance. They have always found it present in babies under two years of age when other certain signs of tetany are to be detected. After the second year, this sign has less significance. In older children, it is commonly met with in cases without past history or present signs of tetany.

Erb's phenomenon of increased motor irritability to the galvanic current was first carefully studied in children by Escherich.[75] The most definite information is obtained from the cathodal opening contraction which in normal infants is not obtained with a current of less than five milliampères, whereas in the presence of tetany a contraction with a current less than this is regularly produced. The cathodal closing contraction has the same significance (Thiemich,[76] Mann[77]). The importance of anodal hyperirritability, in which anodal opening contractions ensue contrary to the normal with a current insufficient to elicit an anodal closing contraction, has been emphasized by von Pirquet.[78] According to Holmes'[79] careful studies anodal excitability is of importance only in the first six months of life.

The Clinical Course of Tetany.—The convulsive seizure usually does not endure more than a few hours, although it may continue for even 24. Periods of intermission occur, the entire attack running its course in two to three days when uninfluenced by treatment. More rarely the carpopedal convulsion becomes permanent. Between the tetanic spasms the special signs may be elicited. Weakness of the muscles involved may occur after a tetanic seizure. Myotonic intention spasms (inability to open the hand after closing same) are described by v. Frankl-Hochwart.

Sympathetic Nervous System.—Hyperexcitability is shown by localized blanching of the skin; sudorrhea, dermographism, spasmodic contractions of the stomach and intestines, also abnormal reactions to adrenalin and pilocarpin (Falta).

Loss of consciousness, or clouded mentality, in the tetanic attack may occur in children in distinction to adults.

The coincidence of *epilepsy* and *tetany* has been remarked by many observers. Either condition may precede the other in its development, or both may begin simultaneously. Inasmuch as the causes of epilepsy and tetany are multiform, in the present consideration only epilepsy combined with tetany and other hypoparathyroid signs and symptoms may be properly included. Such a syndrome is most frequent in epilepsy in children. See excellent discussion of this subject by G. C. Bolton[80] and Falta.[81] A. Bisgaard and P. Növig[82] have recently observed a marked similarity in the enamel defects, protein and ammonia metabolism to those observed in hypoparathyroidism. It is fair to assume that the epileptiform convulsions observed in this disease merely represent, as does tetany, a clinical syndrome.

The **special senses** may be affected. Slowness or absence of pupillary reaction is common in severe tetanic attacks. Differences in pupillary size may occur. Lachrymation is rare (Kahn and Falta). Annular cataract has been described by Garrahan and Belgeri[83] in a case of a girl of four years. Neuroretinitis may be present.

The **ear** may be affected according to Frey and Orzechowski[84] who report a series of cases of tetany combined with otosclerosis.

Diagnosis.—Much of the present confusion as to the nature of tetany and clinical hypoparathyroidism might be avoided if, for diagnostic purposes, only those cases showing true tetany in addition to at least some trophic changes of the nails, skin, subcutaneous tissues, enamel and bones are regarded as a true deficiency condition of the parathyroid glands. Thus tetany of gastro-intestinal origin and idiopathic tetany of really unknown origin are excluded. The same applies to various fleeting spasmophilic conditions in children of which our knowledge is too fragmentary for classification at present. In determining the diagnosis of hypoparathyroidism from this standpoint, added emphasis must be laid upon the general examination, and systemic means of record of the same, and judicial evaluation of the data so obtained. It is well to bear in mind that many of the systemic effects of the deficient parathyroid function closely resemble those of other endocrine deficiencies, particularly when the latter are present in latent form. The *combination* of true tetany and such trophic changes is however of great diagnostic importance. Aside from observation of the actual tetanic convulsion, the determination of the presence of the symptom-complex tetany rests upon the positive Trousseau's sign and the Erb's phenomenon, less certainly upon Chvostek's sign (see above).

Differential Diagnosis.—**Hysteria** may simulate hypoparathyroidism only when the former is present in combination with true

tetany. Hysterical convulsions may be present in tetany but the presence of hysterical stigmata or of the special signs of tetany, particularly Erb's phenomenon, together with trophic phenomena, should easily determine the diagnosis.

Tetanus is distinguished by history of wound or other infection, generally increased reflexes, absence of involvement of the hands, and the classical symptoms of tetany.

Epilepsy must be carefully differentiated. Epileptiform convulsions may occur in the course of tetany. True epilepsy is to be distinguished by the presence of an aura, the loss of consciousness, the post-epileptic stupor or mental disturbances and incontinence of feces and urine. Loss of consciousness is quite rare in the tetany of hypoparathyroidism. The epileptic convulsions of childhood are characterized by absence of galvanic excitability.

Prognosis.—The prognosis of hypoparathyroidism in children is rather dubious. According to Escherich, Thiemich, Falta, *et al.*, a considerable number of tetanic children soon die. Though these children cannot all be said to necessarily have parathyroid tetany, yet it is known that this condition is more serious with regard to life than the simple idiopathic tetanies. Such children are beset with a profound cachexia affecting both psychic and physical development which invites the onset of infections and other diseases. The outlook for gastric tetany is especially unfavorable. Spontaneous recovery, however, frequently occurs. It is well to bear in mind that the parathyroids are organs essential for the continuance of life.

Treatment.—Prophylaxis.—General measures of hygiene and properly conducted infant feeding are of importance in preventing the disease. In thyroid operations due care as to avoiding injury or removal of the parathyroids is essential. Transplantation of the parathyroids has been successful in an increasing number of instances in adult cases but in babies or small children the technical difficulties of such an operation are very great. The writer has been unable to find authoritative statements as to the final success of this procedure in children. It is likely that in the great majority of instances, just as in the case of thyroid transplantation, the implanted parathyroids are rapidly absorbed.

Opotherapy is at present of dubious value. Rarely brilliant results are recorded, particularly when the fresh glands are administered. It is possible that in commercial products deleterious changes ensue in course of manufacture.

The control of the tetanic convulsions is of great importance. The calcium treatment, originally suggested by MacCallum and Voegtlin as curative, is now considered of value only in the symptomatic relief of tetany. Good results are reported by Netter,[24] Göppert,[25] J. Howland and W. McK. Marriott.[23] The latter authors thoroughly studied the effect of calcium with control of the calcium content of the blood, and electrical reactions, and came to the conclusion that administration of calcium salts controls the tetany, increases the cal-

cium content of the blood and causes the galvanic excitability to become normal. The dosage for infants is from 0.5 to 1 gm., preferably as calcium chlorid given in the food. Administration of this remedy in this way is usually unattended by vomiting or other ill effects. Phosphorus and cod-liver oil (recommended by Finkelstein) are known to exert a slight but usually definite effect on tetany. It may become necessary to administer chloral, morphine or chloroform to check the convulsions until the calcium can begin to exert its influence as it does in about three to four days. Subcutaneous injections of magnesium sulphate are recommended by Berend.[85] Thiemich uses 0.5 gm. or 8 mm. of a 2 per cent. solution per rectum, the spasms being thus controlled for six to eight hours. The convulsive excitability is decreased by a prompt evacuation of the bowels and a farinaceous diet, as emphasized recently by Dragstedt's experiments. The control of gastric tetany includes gastric lavage, a concentrated diet, enemata for thirst. Gastro-enterostomy should be undertaken promptly on account of the excellent results reported of late.

INFLAMMATIONS AND OTHER RARE CONDITIONS OF THE PARATHYROID GLANDS IN CHILDREN

Inflammation of the parathyroids may occur as a part of a general infection. Tetany has been observed in a number of other infectious diseases. Tetany of probable hypoparathyroid origin has been reported in typhoid epidemics where seasonal tetany is common. The typhoid fever is here rather determinative than causative. Erdheim reported a case of septic embolism of the parathyroids and tetany in a 13 year old boy dying of sepsis.

Tuberculosis of the parathyroids with tetany has been reported by a few authors, though it is very rare in children and then usually a local expression of acute miliary tuberculosis. Yanase[59] observed amyloid degeneration of the parathyroids in a boy of 14 suffering from tuberculosis of the bones with general amyloid disease.

Hyperplasias of the parathyroids have been reported by Erdheim, et al., in osteomalacia. There is no reason to believe that a condition of hyperfunction of the parathyroid glands is recognizable. Localized connective tissue overgrowths in these organs have been found by various observers without establishing a definite connection with a functional disturbance.

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CHAPTER LXXXIV

THE HYPOPHYSIS

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The hypophyseal apparatus as a whole comprises the hypophysis pharyngei, the parahypophysis and the hypophysis cerebri. The latter is made up of two lobes, the anterior and posterior. The anterior lobe consists of the pars anterior propria, the pars intermedia and the recently described pars tuberalis. The posterior lobe consists of the infundibulum and the pars nervosa.

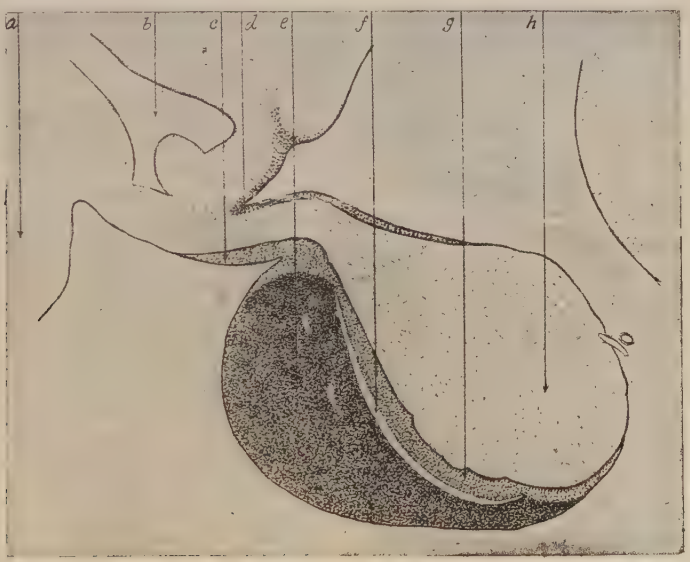

Fig. 144.—Median sagittal section through pituitary of monkey; semidiagrammatic (Herring): *a*, Optic chiasma; *b*, third ventricle; *c*, *g*, pars intermedia; *d*, epithelium of pars intermedia extending round neck of pars nervosa; *e*, pars glandularis seu epithelialis; *f*, intraglandular cleft, lying between pars glandularis (*e*) and pars intermedia (*g*); *h*, pars nervosa.

The hypophysis proper is derived as an evaginated portion of the ectodermal pouch of Rathke, which grows upward under the brain from the pharyngeal epithelium. It is a small oval body weighing, in the adult male or nullipara, about 0.65 gm. In the pregnant state it increases strikingly in size through the development of "gravidic cells." The gland lies in a recess of the sella turcica, being connected with the brain behind the optic chiasma by the infundibular stalk.

The posterior lobe lies in a depression in the anterior lobe roughly resembling the endosperm in a grain of corn. Embryologically it is derived from the infundibular stalk which extends as a downgrowth from the floor of the third ventricle to meet the pharyngeal evagination which forms the anterior lobe. The pars intermedia is derived from the posterior wall of Rathke's pouch. It extends as a thin epithelial layer between the anterior lobe proper and the posterior lobe which it invests. It is often divided by a cleft containing colloid, which represents the original lumen of Rathke's pouch. In the man the pars tuberalis is represented merely by an inconspicuous prolongation of the anterior lobe tissue extending along the infundibulum.

The hypophysis pharyngei is made up of tissue like that of the anterior lobe, being the remains of the stalk by which, embryologically, this structure was connected with the pharyngeal mucosa. It lies in a median position near the junction of the nasal septum and the roof of the pharynx. It is of importance surgically as a source of neoplasms. It probably serves functionally as a part of the anterior lobe, although independent activity has been occasionally ascribed to it.

The parahypophysis is derived from bits of the cranial hypophyseal fundament which often split off during embryonic development to form accessory glands. They are usually confined to the sella turcica. They probably share with the hypophysis proper in the production of hormones.

The blood supply of the hypophysis is derived from the internal carotids and the circle of Willis, and distributed collaterally to all parts. The anterior lobe is highly vascular, the posterior much less so. The veins from all portions discharge into the circular sinus.

Little is known as to the innervation of the hypophysis but both sensory and sympathetic fibers from the carotid plexus have been described. Shamoff has claimed that hypophyseal secretion can be augmented by stimulation of the superior ganglia of the cervical sympathetic nerves.

Histologically, the anterior and posterior lobes are very dissimilar. The anterior is made up of epithelial cells grouped more or less into acinus-like structures permeated by vascular sinusoids. These cells comprise two major sets, the "chromophile," which stain deeply, and the "chromophobe," which remain clear. The latter are also referred to as chief, principle, or reserve cells. The chromophile cells are designated acidophilic or basophilic depending upon their relative affinity for acid or basic dyes. The genetic and functional relationships of these various cell types are not well understood, but the granules which are conspicuous in the acidophile cells are thought by many to represent the secretory antecedents of the gland. They are often conspicuous in acromegaly. The pars intermedia cells are also epithelial but differ from those of the anterior lobe in their smaller size and lack of conspicuous acidophilic granules. In the deeper portions of the gland the cells tend to form small vesicles somewhat like those of the thyroid gland, which they resemble also in being filled with

eosinophilic colloid. Most recent investigators regard this colloid as a true secretion of the gland. It is thought by Herring to pass into the posterior lobe from which it is discharged through the infundibulum into the third ventricle. There is some evidence, also, that it is discharged directly into the blood stream.

The pars nervosa consists chiefly of a rather dense mass of neuroglia containing few blood-vessels. There are no demonstrable nerves. Dark greenish-yellow pigment is often found free in the interstices between the neuroglia fibers and in their cells. Cells of the pars intermedia tend to migrate into the adjacent parts of the posterior lobe. Globules of colloid previously mentioned as derived from the pars intermedia are found among the neuroglia fibers. Experimental investigations as to the functions of the hypophysis have been chiefly along two lines, namely, studies of the effects of injections of extracts and of the effects of extirpations of the various parts of the organ. But these have been supplemented by many studies of morphologic changes of the organ in relation to various bodily conditions.

Experimental ablation of the hypophysis has given many contradictory and confusing results in the hands of different investigators. It is generally but not unanimously accepted that complete removal of the gland is a fatal procedure. The animal dies within a few days, after exhibiting such symptoms as hypothermia, ataxia, rapid emaciation and diarrhea. Very similar results have often been reported following the extirpation of the anterior lobe alone.

Removal of the posterior lobe may produce no effect except possibly some tendency to adiposity. Removing a large portion of the anterior lobe in a young animal, according to the preponderating weight of evidence, leads to retardation of growth, especially that of the skeleton, and prevents maturation of the gonads, thus leading to *infantilism.* Mental depression, somnolence, tendency to obesity and lowered metabolic rate result. The carbohydrate tolerance is increased, though whether on account of anterior lobe or incidental posterior lobe involvement is a debated question. The thyroid, thymus and adrenal cortex undergo hyperplasia. Life is shortened.

In older animals anterior lobe injury induces hyperglycemia and glycosuria, obesity and progressive atrophy of the gonads with resulting sex depression.

On the whole, extirpation experiments indicate that the hypophysis, particularly the anterior lobe, plays an essential part in growth and maintenance throughout the body, but especially in the bony tissue, the gonads and the brain.

Oliver and Schafer discovered that extracts of the hypophysis as a whole cause a rise of blood pressure. Howell subsequently discovered that the pharmacodynamic substance is found almost entirely in the posterior lobe. It is apparently derived originally, however, from the pars intermedia. Of recent years the pharmacology of posterior lobe extracts has been studied intensively. The most elaborate investigations have been made by Houssay of Buenos Aires. The

results of such studies can largely be comprised in the single statement that the extract stimulates cardiac and smooth muscle throughout the body. Thus the uterus, the intestine, the bladder and the blood vessels are thrown into a state of higher tonus or augmented peristaltic activity. In a general way the effects are similar to those of adrenin but differ in that the reaction is more prolonged and almost always excitatory whereas adrenin causes depression of function in the gut and other structures having inhibitory sympathetic innervation. There is a body of fairly convincing evidence that such extracts may "sensitize" tissues so that they respond more actively to sympathetic nerve stimulations.

The clinical use of pituitary extracts (pituitrin, hypophysin, etc.) depends upon their property of stimulating smooth muscle. In obstetrical practice the extract has come into wide use in the treatment of uterine inertia. Similarly, it may be advantageously used in meteorism or any atonic condition of the intestines, and in cases of urinary retention due to loss of bladder wall tonus or contractility. In such conditions the lack of toxicity and the action independent of nervous factors may be important. It should be noted, that continued daily injections may be deleterious after a time.

In 1910 it was reported by Ott and Scott that pituitary extract has a striking effect in increasing mammary gland flow. The observation was readily confirmed and hopes were entertained that an efficient galactagogue had been found. It was soon learned, however, that secretion proper was little influenced, and that the readier outflow was due to stimulation of the intrinsic smooth musculature of the gland. This property is occasionally of practical use in stimulating a free flow of milk in cases in which the infant has difficulty in nursing. The drug has to be administered hypodermatically or intramuscularly, and the effect is transitory. (More recent evidence indicates that intranasal or sublingual administration may be effective.)

Magnus and Schafer discovered that under certain experimental conditions pituitary extract causes a brief augmented secretion of urine accompanied by vascular dilatation in the kidneys. This observation was abundantly confirmed and led to much theorizing to the effect that the hypophysis has a normal function of stimulating the kidneys. Like many other endocrine theories, however, this one proved premature. In normal individuals and especially in various conditions of polyuria, posterior lobe extracts actually cause a marked decrease of urine volume. Therapeutically this finding has proved valuable in the treatment of diabetes insipidus. In some instances favorable results have been obtained by administering gland substance by mouth, but in most cases hypodermatic or intramuscular injections must be employed. The effects in favorable cases are very striking. A polyuria of 10 liters a day may be reduced to two, and, what is important, the patient obtains an uninterrupted night's sleep.

Such observations suggest that the pituitary gland through its internal secretion normally keeps a check on urinary secretion. The

likelihood that such is the case is increased by the observation that injuries of the organ may lead to extensive polyuria. Marañón has reported a clinical case that is virtually a crucial experiment on this point. A boy received an accidental bullet wound in the mid-frontal region. At first no nervous or psychic changes were noted. Later, he showed all the signs of Fröhlich's syndrome together with marked diabetes insipidus. No treatment affected the diuresis except injections of pituitrin. This treatment was brilliantly successful, reducing the urine from nine liters to one liter a day. An attempt to remove the bullet proved fatal. At autopsy the bullet was found in the region of the infundibulum. The stalk of the pituitary body was interrupted by cicatricial tissue, apparently preventing discharge of the secretion into the third ventricle. The pituitary body, itself, was unharmed.

The use of anterior lobe substance in the hands of numerous investigators has frequently yielded negative results. Of recent years, however, feeding experiments have been reported by a number of investigators which indicate that such material may serve as a stimulant to growth and to sexual development. Robertson has isolated a substance "tethelin" which has been reported to accelerate the growth of mice; the growth of transplanted neoplasms was also augmented. Similar results have been obtained from feeding anterior lobe substance to tad-poles. The retardation in growth of such larvæ which results from hypophysectomy can, by such feeding, be entirely prevented (Smith). The experimental basis is thus established for the clinical use of anterior lobe substance in cases of retarded development of children. Although occasional favorable results have been reported much remains yet to be done to establish the place of such material in practical therapeusis.

A condition of superabundant pituitary secretion may arise spontaneously through hypertrophy or the development of adenomata of the gland. If the hyperactivity occurs in childhood a condition of general body overgrowth, gigantism, results. In cases arising after the closure of the epiphysis the overgrowth is more restricted, the connective tissues of the extremities and of the face being especially affected, giving rise to acromegaly. Cranial skiagrams or post-mortem examinations in such cases ordinarily reveal an enlarged sella turcica. Direct examination of the gland in the earlier stages of the disease usually shows a condition of hypophyseal hypertrophy more or less restricted to the anterior lobe. In the later stages an atrophic or cystic condition may be found. Hypertrophy of the anterior lobe results in pressure with consequent depression of function of the remainder of the organ. Numerous exceptions to the preceding statement have been taken. Cases of undoubted acromegaly have been described in which the hypophysis appeared to be normal. In other instances no change in size has been observed but the acidophilic cells of the anterior lobe have been markedly increased. To complicate the situation still further, however, similar degrees of acidophilia

are observed without any tendency to acromegaly. The most convincing evidence that hyperfunction of the pituitary is causally related to acromegaly lies in the amelioration of symptoms that may be brought about by partial excision of the gland. Whether, however, the disease is due to *hyperpituitarism* as believed by Marie or to *dispituitarism* as maintained by Roussy is yet an open question.

Acromegaly.—Acromegaly occurs more frequently in women than in men. It usually begins between the ages of 20 and 40. There appears to be an hereditary factor in the disease although, owing to the low fecundity of acromegalics, the disease bearing strains tend to be self-limited. The anamnesis often reveals disturbances of metabolism, infections or intoxications (Barker). The symptoms of the disease are so characteristic that it is usually easily diagnosed. The onset is insidious. Often the first recognized change is an enlargement of the hands, feet or head. The patient's attention is drawn to the condition by his needing larger gloves, shoes or hat. In other cases, however, the onset is first detected by the physician, the patient presenting himself with such symptoms as headache, apathy, sleepiness or epileptiform convulsions suggestive of intracranial pressure. Sexual depression, amenorrhea or menstrual irregularities in females and diminished libido or potentia in males usually is present, often long in advance of bodily deformity.

The changes in the skeleton are characteristic. The facial bones are more affected than those of the cranium, resulting in a coarse, large face with large nose, bulging glabellæ, protruding malar bones and thick, projecting chin. The lips and tongue are also thickened. The teeth do not enlarge, but the overgrowth of the jaws leads to characteristic widening of the interdental spaces. The ears are enlarged. The skin is thickened, dry and wrinkled. The hair, beard and eyebrows are coarse. The laryngeal cartilages share in the general hypertrophy resulting in a hoarse, low-pitched voice. The spade-like, broad, thick hands and "sausage fingers" are very characteristic. The wrists, forearms and arms are approximately normal. The lower limbs are affected much as the upper. In the thorax the clavicles are enlarged, and there is kyphosis of the lower cervical and upper thoracic spine. The anteroposterior chest diameter is relatively great as compared with the lateral. The abdomen projects and the hips are broad. The penis or labia are enlarged, but the testes or uterus and breasts are more or less hypoplastic.

Headaches are frequent and often severe. They are often accurately localized by the patient in the hypophyseal region. They may however, be occipital, frontal or diffuse. The mental depression previously mentioned may be very pronounced. The patient talks but little, and the speech is heavy and slow. Occasionally outspoken psychoses may develop. Either *grand* or *petit mal* may occur. Bilateral hemianopsia, indicating mesial pressure on the optic chiasma, is a very characteristic symptom. Diminishing and interlacing of the visual color fields are also significant findings. A generalized

splanchnomegaly is common. Glycosuria is noted in 30 to 50 per cent. of the cases, and there may be polydipsia and polyphagia suggestive of diabetes mellitus. The thyroid is usually abnormal, showing struma or atrophy. Thymus hypertrophy and status lymphaticus have also been noted.

The diagnosis of the fully developed disease is not difficult, but the earlier stages are often not recognized. Complaints of severe headache, of neuralgic pains in the limbs and of genital disturbances in early adult life should always excite suspicion, especially in families of tall people (Barker). In doubtful cases skiagrams of the head should always be made. Characteristic acromegalic signs to be looked for are enlarged sella turcica, erosion of the clinoid processes, enlargement of the frontal sinuses, irregularity in cranial thickness and exaggeration of the external occipital protuberance.

Acromegaly must be differentiated from several other conditions. (1) In myxedema the soft parts are infiltrated; bone development is arrested instead of augmented; often there is dwarfism and the facies is characteristic. (2) In Paget's disease the cranial rather than the facial bones are affected; the bi-temporal rather than the bi-malar diameter is increased; the face is somewhat triangular rather than hexagonal in shape. The shafts of the bones rather than the acra are enlarged. Calcification of the arteries is common, and the disease is characteristically one of advanced life. (3) In rickets the classic bone symptoms, the later closure of the fontanelles, the senile facies, the absence of acral enlargement and the onset in early life are the important differential points. (4) Leontiasis ossea may be differentiated by the relatively sunken nose, the rapidity of hypertrophic changes in the facial and cranial bones, the earlier onset and lack of enlargement of the tongue. (5) Hypertrophic pulmonary osteoarthropy can be differentiated by the failure of the soft parts to share in the bone hypertrophy, by the incurved nails, the enlargement of the finger tips, the wrist joints and the toes and ankles, the unaffected lower jaw, the absence of cerebral and genital symptoms and the association with intrathoracic diseases.

Treatment.—The only rationally established treatment for acromegaly in the active stage is that directed to decreasing the amount or function of the hypophyseal tissue. If the size and position of the tumor are favorable hypophysectomy may be attempted with some hope of success. When surgery is contra-indicated radiotherapy offers some hope. Pure hyperactivity of the gland probably seldom occurs. Pressure leads to depression of the posterior lobe and ultimately of the hypertrophic anterior lobe itself. In a rough way the transition from the hyper- to hypo-active state can be recognized by a change in the patient from low to high sugar tolerance. Occasionally organotherapy has been reported as relieving hypophyseal deficiency. Whole gland preparations should preferably be used. Any indicated dosage is tentative. A trial period of desiccated pituitary substance (gr. v, t.i.d.) may be given and gradually increased. Such medication

is not without danger. It may stimulate nevi or benign neoplasms to malignant growth (Timme).

A condition of frank *hypopituitarism* is easier to deal with and is of more immediate interest to the pediatrician. While lesser degrees of the condition doubtless often exist unidentified and play an important part in the production of metabolic anomalies, interest centers particularly in *Fröhlich's syndrome* or *Dystrophia adiposogenitalis*, and in *diabetes insipidus*.

Dystrophia adiposogenitalis is a well-marked clinical entity which may become manifest either in early childhood or later in life. It is due usually to destructive tumors of the hypophysis affecting especially the posterior lobe. Marañón's traumatic case referred to previously and the experimental production of the condition by partial extirpation of the hypophysis (Cushing, Aschner) seemed to fix the etiology rather definitely. More recent work, however, showing that the same conditions may be brought about by injury of the tuber cinereum cast doubt upon the matter.

When the condition is due to tumor, several well-marked pressure symptoms usually develop. These include headache, vomiting, epileptiform attacks, mental disturbance, optic atrophy, bitemporal hemianopsia and contractions of the visual fields. Radioscopy shows changes in the sella turcica and lesions in the body of the sphenoid bone. The details of these changes vary according to the size and position of the tumor.

In addition, several symptoms due to lack of pituitary secretion arise, giving an adult body-weight of 200 to 300 lb. or more. The fat is characteristically most abundant as a zone including the lower abdomen and thighs. Under organotherapy this fat may be either lessened in amount or distributed more normally (Beck).

The skin is smooth and delicate, sometimes giving a beautiful "peaches and cream" complexion. Sometimes it is wrinkled and occasionally may resemble that of myxedema or scleroderma. The axillary and pubic hair is sparse, and often the latter has more or less the distribution characteristic of the opposite sex.

Other anomalies of the sex stigmata occur. If the disease develops early the genitalia retain their hypoplastic, infantile state. If it develops in the post-pubertal stage retrogressive structural changes and depressed functions of the sex organs appear. The axillary hirci, pubic crines and the eyebrows tend to fall out.

A depression of skeletal development often leads to actual *dwarfism*, when the disease begins in early life. The skeleton of the male, too, tends to approach the female type, adding to the feminine appearance brought about by the distribution of the fat and by the gracile extremities and tapering fingers. The voice tends to have a feminine pitch. Various degrees of diabetes insipidus (*cf. infra*) are often present. Various other anomalies probably referable to pluriglandular defects are often present. Among these are tachycardia, asthenia, low blood pressure and temperature, abnormal pigmentation and myxedema.

In the light of experimental evidence it is probable that the growth and genital anomalies are due to hypofunction of the anterior lobe, whereas increased carbohydrate tolerance, obesity, diabetes insipidus and possibly vascular hypotension depend upon depressed posterior lobe functions. As evidence in this connection a case reported by Simmonds is instructive. A man of 21 years, 110 cm. in height and well proportioned, had no beard nor pubic crines. The gonads were infantile. At autopsy the anterior lobe of the hypophysis was found atrophic while the remainder of the organ appeared entirely normal, as did the endocrine glands other than the testes.

Diagnosis of dystrophia adiposogenitalis, in the presence of the above mentioned symptoms, is usually easy. In the earlier stages, or in atypical cases, however, it may be attended with difficulty. Frölich's syndrome is suggested by any of these conditions: temporal limitation of the visual fields, menstrual disturbances, obesity of rapid development, intracranial pressure symptoms and diabetes insipidus. The diagnosis can usually be completed by the examination of cranial skiagrams.

Differential diagnosis necessitates the consideration of brain tumors, hydrocephalus, epilepsy and diseases of the base of the skull. Other endocrine anomalies, Dercum's disease, myxedema, cretinism, status thymo-lymphaticus, other types of dwarfism and chlorosis may also present confusing pictures.

Treatment.—The associated intracranial pressure symptoms should be considered as such. Treatment directed toward the relief of the hypophyseal deficiency is largely still in an experimental stage. Excellent results from the administration of desiccated whole gland hypophyseal preparations have been reported, as have also many failures. Thyroid preparations may give favorable results. A great deal more of clean cut organotherapeutic experimentation is needed. It should be remembered that the tumor causing the symptoms may be a gumma. In that case, the treatment is, of course, antiluetic.

Diabetes Insipidus.—Of recent years the evidence has strongly tended to the conclusion that this condition is often due to hypofunction of the posterior lobe of the pituitary. It can be produced experimentally by destructive lesions of this structure, and brilliant therapeutic results have been obtained by injections of pituitary material. The topic is treated at length in Vol. II, page 804.

Surgical Considerations.—Of recent years the hypophysis has come into the realm of practical surgery. The organ lies in the sella turcica. It is separated from the cranial fossa by the dura mater which forms the diaphragm and lining of the sella. The middle of the diaphragm is perforated by the infundibulum. From an operative standpoint the relations of the arachnoid are important. Usually it surrounds the infundibulum as a sheath and extends downward only to the cranial side of the dura which covers the sella. Only rarely does the arachnoid pass beneath the diaphragm to invest the hypophysis proper. Hence if the diaphragm is not perforated during the operation, the chances of invading the subarachnoid space are slight.

The anterior and posterior lobes of the organ can readily be separated. There is a natural plane of cleavage in the cleft of the pars intermedia, representing the original cavity of the buccal evagination from which the pars and the anterior lobe were derived. Splitting apart of the two lobes in this way does not give a true physiologic separation since the posterior lobe is covered with a layer of epithelium genetically like that of the anterior lobe. The gland can be approached in several ways. Intracranially it may be reached through the anterior fossa or through the temporal fossa. Transphenoidally, access is obtainable through the mouth or through the nose, either by a supranasal or an infranasal route. The transphenoidal has been the approach most favored by surgeons up to the present time. Operative mortality statistics have not yet accumulated to a significant extent. Results reported give a varying mortality from 8 to 40 per cent. or higher. The Fröhlich type of hypophyseal cases has at present the best operative prognosis.

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CHAPTER LXXXV

PINEAL GLAND

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The pineal body is a cone-shaped structure attached by a short stalk to the posterior boundary of the dorsal surface of the third ventricle. It is thus in relation to the aqueduct of Sylvius and the vena magna Galeni, and hence, potentially could readily exert an influence on the local circulation of both the blood and cerebrospinal fluid. The cavity of the third ventricle extends a short distance into the gland, forming the *recessus pinealis*. The pineal body rests on the mid-brain in a depression between the superior colliculi. It is dark red in color and is about 4 by 6 mm. in diameter. The statement has often been made that it is larger in females than in males, but in rats, at least, E. R. Hoskins has found no sex difference. The organ reaches its maximum development in children at about the seventh year after which progressive involution occurs. Contrary to statements often made, involution does not usually progress to an extreme degree. McCord found it no further advanced at 90 than at 13 years.

Both phylogenetically and ontogenetically the nature of the pineal fundament is questionable. By some it is regarded as primarily sensory rather than glandular in its potencies. Tilney and Warren, however, dispute this, maintaining that the region of the diencephalic roof from which the body originates is fundamentally glandiferous, the sensory affinities being confined to the terminal vesicle. In certain lizards this forms the so-called parietal eye.

Histologically, the pineal body consists of ependymal cells scattered in a framework of neuroglia and connective tissue, more or less divided into lobules. Within the lobules are cyst-like structures and in the older stages especially, acervulus or brain sand is found. This consists of crystalline masses of calcium phosphate and calcium carbonate. The ependymal cells are of irregular shape. They contain a considerable amount of pigment as well as lipoid inclusions and typical mitachondria. The blood-vessels are large and sinusoidal.

Most of the apparently significant data regarding the functional aspects of pineal biology have come from clinical rather than experimental sources. Injection experiments have given little evidence that the organ forms any pharmocodynamic substance. Blood pressure is slightly lowered by pineal extracts as it is by extracts of various neutral tissues. McCord has recently reported, however, that

pineal extract does exert a striking influence on the pigment cells in the skin of tad-poles.

Feeding experiments have given varying results. Dana and Berkeley fed pineal powder to young cats, rabbits and guinea pigs over a period of two and one-half to five months. The experimental animals gained in weight from 7.5 to 20 per cent. more than the controls. McCord got similar results with puppies, guinea pigs and chicks. His guinea pigs gained 23 per cent. more than the controls. Some evidence of earlier breeding was also obtained. Boehm and also E. R. Hoskins report negative or conflicting results. The experiments should be extended.

Clinically, Dana and Berkeley reported beneficial effects from feeding pineal gland substance to backward children. Intelligence seemed to be stimulated, but there was no improvement of physical development. Goddard later continued the experiments and reported negative results. He concluded that the value of pineal medication was in the end nil. There is little justification at present for pineal medication.

Strangely enough, extirpation experiments have given results much like those of gland feeding. The earlier investigators used dogs and rabbits from which the pineal can be extirpated only with much surgical difficulty. A few suggestive instances of augmented growth were observed. In chicks such results proved more easily attainable. Dandy elaborated a careful technique for pinealectomy in dogs and in 1912 and 1915 reported negative results. Horrax repeated the experiments, using principally guinea pigs and rats in which the gland is more easily accessible. His pinealectomized animals showed materially hastened sexual development.

Tumors.—In the pineal body cyst formation and tumors are not uncommon. Of the latter, teratomata are most usual, but gliomata are also not infrequent. The anatomic possibilities of local circulatory disturbances from such tumors have been previously suggested. The possibility of nervous involvement is also extensive.

Symptoms.—Pineal neoplasms are associated with three categories of effects, namely, general intracranial pressure symptoms, certain focal symptoms and somatic changes usually ascribed to endocrine factors.

The signs of increased cranial pressure are ordinarily due to the hydrocephalus resulting from occlusion of the Sylvian aqueduct rather than to the mass of the tumor, *per se*. Among these are vomiting, headache, vertigo, choked disc, somnolence and certain mental chan es. Bradycardia is unusual.

The focal symptoms arise from interference with mid-brain structures, particularly the corpora quadrigemina, giving rise to paralysis of oculomotor, trochlear and abducens nerves. Diplopia is usually observed and occasionally nystagmus and exophthalmos. Pressure from the dilated third ventricle on the optic chiasma not infrequently results in optic atrophy. Other cerebral nerves such as

the glossopharyngeal, facial and acoustic may also be involved. Pressure on the cerebellum may give rise to ataxia as a prominent symptom.

Of the changes supposedly ascribable to endocrine disturbance, polyuria and polydipsia may be due to pressure on the hypophysis or on the neural structures adjacent to it. The cause of the polyphagia which also may be a prominent symptom is entirely problematical. More particularly characteristic are the group of symptoms for which the name "macrogenitosomia precox" has been suggested.

The syndrome usually occurs in boys before the age of puberty. Associated with a general bodily overgrowth is a striking augmentation of the size of the primary sex organs. These are frequently as large in young children as in the normal adult and both pubic and axillary hair is similar in extent and abundance to that of maturity. Mental precocity is also sometimes noted.

In all cases so far studied autopsy has revealed a neoplasm of the pineal gland. But whether these changes are due to a primary pineal factor or, as Barker suggests, to abnormal nervous manifestations playing upon other endocrine glands is not yet determined.

The **diagnosis** of pineal tumor is based upon the above mentioned signs of intracranial pressure, mid-brain focal symptoms and abnormal height, growth of hair, obesity, somnolence and sexual precocity, both physical and psychic.

In the **differential diagnosis** it is necessary to distinguish the pineal disorder from: (*a*) Hypophyseal tumors (bi-temporal hemianopsia, skiagram of the sella turcica); (*b*) other causes of sexual precocity (neoplasms of the gonads and of the adrenal cortex); (*c*) tumors of the mid-brain or cerebellum, and (*d*) chronic internal hydrocephalus.

As to **treatment,** palliative surgery (decompression) should be considered, but there is little evidence of favorable results yet available to encourage such measures.

On the whole the functional significance of the pineal gland, either in health or disease, is an open question. Further investigations are needed as regards both its physiology and its pathology. Whether it is merely a vestige or a functional organ is still under debate with the evidence tending perhaps more strongly to the latter alternative.

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CHAPTER LXXXVI

HYPERGENITALISM AND HYPOGENITALISM

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In addition to the condition of macrogenitosomia precox, described in the chapter on the pineal gland, a condition of *pubertas precox* or precocious sexual development may be encountered. This may develop as a result of primary hypergenitalism, proper, or in association with tumors of the adrenal cortex, usually hypernephromata. Aside from the concurrent presence of the adrenal neoplasm, cases of primary and secondary hypergenitalism are closely similar and can conveniently be treated together.

The suprarenal type varies in its manifestations depending upon the age of incidence. For convenience of description the cases can be divided into three groups, but it should be borne in mind that the types actually grade more or less into one another.

When the adrenal hypertrophy occurs during fetal life the condition of *pseudohermaphroditism* develops. In such cases the internal genitalia are likely to be somewhat hypoplastic, but the external sex characteristics resemble those of the opposite sex. In the type simulating the female, an enlarged clitoris, urethra of the male type, prostate fairly well developed and a configuration of the vulva like a scrotum may simulate conditions in the male so closely that the individual is regarded as a boy by the parents and the subject, also. Conversely, female characteristics may appear externally in subjects possessing testes although usually not in cases of adrenal origin.

Hypernephromata beginning early in post-natal life may give rise to *pubertas precox*. In the earlier months or years the children appear to be entirely normal. Then abnormal accumulations of fat begin to appear, especially on the hips, lower abdomen and mons veneris. Rapid growth and increasing strength simultaneously are noted. Intellectually, the subjects are likely to be somewhat dull but may be bright and precocious. At this stage the children given an impression of abundant health and well being. All the phenomena of puberty begin to develop rapidly, and at an age of five or six years, or even less, full sexual maturity may have been attained. The condition has been described in both sexes, but females predominate. Glynn collected 17 cases that came to autopsy. Of these all but three were girls. The symptomatology is largely indicated by the preceding statement that sexual maturity is attained. This may or may not be symmetrically developed. For instance, mammary hyperplasia may fail to

keep pace with other manifestations of the condition. Further description given under the succeeding caption "primary hypergenitalism" is equally applicable to this type.

In a third type, the adrenal neoplasm appears only after puberty. This may result in the condition known as *virilismus* or *hirsutismus*. Women between the ages of 15 and 20 years are most often affected, but a later incidence may be encountered. At the initial stage menstrual irregularities or amenorrhea, nausea, vomiting and obesity are the most striking manifestations. The muscular development and physical strength are often excessive for the sex. The patient is likely to consider herself in exuberantly good health. Mentally, also, a sort of hypersthenia may develop, the patient becoming egotistical, overbearing and impatient of opposition. The sexual proclivities may become excessively marked, but such is by no means always the case. In fact, a condition of "maleness" that is frequently superposed upon the fundamental femininity is likely to result in a depression of the sex tendencies. This masculinization manifests itself not only in the augmented strength previously mentioned, but also as regards growth and the distribution of hair. A moustache and beard develop; hair appears on the abdomen, chest and extremities. The transverse pubic crines of the female is superseded by the masculine distribution. These changes in the aggregate constitute *hirsutism*. Aside from hypertrophy of the clitoris, the external genitalia are likely to remain normal. The ovaries, however, are usually small and hard. A general tendency to pigmentation soon begins to appear. This is probably to be ascribed to an approaching failure of normal adrenal functioning.

Although such cases of third stage hypergenitalism are most frequently seen in females, a few cases have been described in the other sex. In such cases, however, the tendency is not toward sex inversion but to augmentation of the masculine attributes.

The conditions of bodily well being are usually temporary. Within a few months other symptoms strongly suggestive of Addison's disease are manifested. Among these are asthenia, low blood pressure, melancholia and frigidity. Albuminuria occurs. Nerve involvement by the growing neoplasm gives rise to drawing and shooting pains in the trunk. By this time the presence of a retroperitoneal tumor is generally easily discovered. Death ordinarily soon follows.

The diagnosis in the later stages is generally easily made from the presence of a large and readily palpable tumor. In the absence of this, the diagnosis may be reached from the association of the above described sex anomalies with signs of metastasis in the lungs, the occipital cranium or the clavicles. In the paroxysmal pains absence of nephrolithiasis and paresthesias in the region of distribution of the lumbar plexus, with hematuria and fever are suggestive. The possibility of an early diagnosis by means of an exploratory laparotomy should be kept in mind. If the neoplasm is unilateral and is discovered prior to metastasis, its removal offers a hope of cure. Otherwise, the prognosis is extremely poor.

Hypergenitalism of adrenal origin is to be differentiated from macrogenitosomia pinealis by the appearance of the roentgenogram, absence of choked disc and other signs of intracranial pressure.

Primary Hypergenitalism.—In addition to those due to neoplasms of the pineal or adrenal glands, cases of hypergenitalism have been described in which the etiologic factor was apparently an hypertrophy or neoplasm of the gonads. In such cases sexual maturation may occur in early childhood. This presents the usual phenomena seen in adults and may be otherwise than in its early incidence apparently quite normal in its manifestations. Neurath in 1909 was able to collect 126 cases of hypergenitalism, 83 in females and 43 in males. He included, however, both the primary and the secondary forms. According to these studies, the sexual precocity begins to manifest itself early, commonly in the second year. Occasionally, however, it appears earlier. Several cases of *menstruatio precox*, for instance, have been reported as beginning at birth. The external genitals grow rapidly and may reach adult form and size within a few months. The growth and distribution of hair resembles that of an adult. Skeletal development is rapid. A large proportion of the boys affected develop partial gigantism, but on account of the early closure of the epiphyseal junctures which generally takes place, the final height is likely to be below normal. Both sets of teeth appear prematurely. The intelligence may remain infantile. In any case it does not ordinarily keep pace with the sexual development. Children so affected demand close attention. The combination of well developed sex impulses with very youthful judgment pre-disposes to unfortunate practices and injurious results.

That the hypergenital manifestations are due in some cases specifically to conditions in the gonads is shown by a case reported by Sacchi. In a child of five years, adult male sex stigmata began rapid development. Soon adult conditions were reached. A beard developed and hair appeared on the body and the extremities. The external genitals were large and the voice deep-pitched. In the ninth year a tumor of one testicle was removed whereupon a marked regression of the sex stigmata took place. The beard and body hair dropped out; the external genitals decreased in size; the sex manifestations ceased; and the voice regained its juvenile pitch. A somewhat similar case in a girl was described by Riedl. This was marked particularly by precocious menstruation. After the removal of an ovarian sarcoma, the menstruation ceased.

That heredity may possibly play a part in such conditions is indicated by a case described by Bodd. The subject began to menstruate regularly at the end of her first year. In her eighth year she became pregnant and gave birth to an infant weighing 3500 gm. The latter exhibited a striking condition of pubertas precox. Axillary hirci and pubic crines were well developed; the mammary glands contained milk.

Agenitalism (Eunuchism).—The operation of castration has been practiced upon young males, both animal and human, since

earliest antiquity. Consequently there is a large body of popular lore as well as of scientific literature upon the subject. On the other hand, there is available but little reliable information concerning females. Such evidence as we have indicates that oöphorectomy performed in early years results in augmented height, infantile genitals and failure of the breasts and other secondary sex characteristics to develop. As is well known from extensive surgical experience the operation in adult women results in reversion or atrophy of the genitals and breasts and the various phenomena of the menopause.

The symptoms of gonadectomy in males depend upon the age of the subject at the time of operation. When this is performed before the onset of puberty, the penis, prostate and seminal vesicles remain small, and libido and erections do not appear. In short, the subject remains sexually infantile. When castration is performed after puberty there is a partial reversion to the infantile condition. The phallus shows some degree of atrophy, but much less than does the prostate. The sex impulse may be lost or may be to a considerable extent retained. Coitus and ejaculation of prostatic secretion can still take place.

Castration as a religious rite has been practiced by a Russian sect, the Skopzi. Tandler and Grosz have studied these subjects at length. Two types of the eunuchs can be distinguished. The members of one group are tall and spare; the other, obese. In the latter, the fat has a peculiar distribution. The excessive deposit on the hips, breasts, lower abdomen, thighs and mons veneris gives a feminine appearance to the subjects. The deposition of fat in the upper eyelids gives the face a sleepy aspect.

The average height of the eunuch is greater than normal, due in part, at least, to delayed closure of the epiphyseal junctures. The head is small; the occiput, flattened; the upper edge of the orbit, prominent; and the sella turcica large. The pelvis is broad. Genu valgum is common. The skin is pale and sallow and often wrinkled so that the subject has the appearance of premature senility. The hair of the head is normal but is sparse or absent in other situations. The pubic crines, which are usually present to some extent, have the transverse feminine arrangement. The larynx remains small so that the juvenile high-pitched voice is retained. Psychically, eunuchs lack in aggressiveness, but otherwise vary little from normal. Although popularly supposed to be feminized, such individuals are more accurately described as sexually infantile but somatically adult.

Hypogenitalism (Eunuchoidism).—Grading into the condition of absolute eunuchism are various degrees of partial gonadal insufficiency giving rise to hypogenitalism. Eunuchoidism is classified as "early" or "late" depending upon whether recognizable before or only after puberty. Although occasionally described in females the great majority of the eunuchoids are males. As regards the latter, the defect is apparently not in the spermatogenic tissues of the gonads, but in the lack of hormone producing elements, the interstitial cells of

Leidig. In cryptorchism, when the Leidig cells are normal, the youth develops at puberty the various sexual characteristics of the male. By ligation of the vas deferens or by Roentgen radiation of the testes the spermatogenic cells can be depressed or destroyed leaving the interstitial cells with more or less functional integrity. In such cases sterility is produced but usually slight if any degree of hypogenitalism.

Pure eunuchoidism is seldom if ever seen. Either primarily or secondarily various of the other endocrine organs are affected giving rise to such conditions as *dystrophia adiposogenitalis*, *geroderma dystrophica*, etc. On the other hand, in the literature cases of apparently true eunuchoidism are found under such captions as *infantilism with gigantism*, *obesity of genital origin*, *infantilism tardif*, etc.

Just as in the case of castrates, there are two types of eunuchoids, the *tall* and the *fat*. Most eunuchoids in whom the glandular defect is primarily in the gonads belong in the tall class. Even the fat subjects, however, are at least of average stature. The symptoms of hypogenitalism vary merely in degree, not in kind, from those of agenitalism. If the condition is due to aplasia of the gonads, such as is often seen in cryptorchism, the scrotum and penis remain smaller than normal. The cremasteric reflex is not well developed. The facial, body and pubic hair is sparse or lacking. The voice remains more or less high-pitched. The skin, especially that of the face, is somewhat pale and delicate. In cases in which the hypogenitalism succeeds a normal condition there is a tendency to reversion to the conditions just described. The actual degree attained is quite variable. In some cases the onset of late eunuchoidism may be quite rapid. The condition may be merely temporary, to be followed by a return partially or completely to normal. This is in all probability to be ascribed to the regeneration of the interstitial cells with restoration to the circulation of the genital hormone. As etiologic factors in late hypogenitalism trauma and infections, particularly syphilis and gonorrhea, seem to be the most important.

True primary hypogenitalism is to be differentiated from *dystrophia adiposogenitalis* by the absence of signs of hypophyseal involvement, such as enlarged or eroded sella turcica, hemianopsia, optic atrophy and other signs of intracranial pressure.

The **treatment of hypo- and agenitalism** is still in the experimental stage. There is possibly some slight scientific basis for the widespread belief that the administration of testicular preparations is helpful in restoring virility. Likewise, in the female, ovarian material is more or less useful in the establishment of normal conditions. In males the use of adrenal cortex substance is theoretically indicated in hypogenitalism by way of stimulating the gonads, but little information as to the practical value of such treatment is available. Transplantation of gonad grafts has been reported at times to give almost brilliant results. Graphic evidence that such grafts can restore a considerable degree of somatic normality has been presented by Wheelon and Shipley. The subject is in need of further clean cut scientific investigation.

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CHAPTER LXXXVII

INFANTILISM

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I. INTRODUCTION

The term "Infantilism" was first introduced and made use of by Lasègue who understood by it the cessation of development of the individual at the stage of the child both psychically and corporeally. We may accept this definition of infantilism in its broad sense and for convenience of consideration subdivide the latter into subgroups, according to our conceptions of its etiology. The French writers, particularly, have interested themselves in the question of skeletal infantilism, dwarfism or nanism, and have distinguished two forms of infantilism, the first the type of Lorain[33] described in the year 1871 and characterized by so-called dystrophic degeneration, as shown by the general arrest of development rather than involvement of any special organ or system. As a consequence the individual is usually undersized, delicate, may show the adult proportions of the body but exhibits also a genital dystrophy and frequently subnormal mentality. In other words, the individual is an adult in miniature. In this type general etiologic causes are recognized such as hereditary intoxications resulting from lues, malaria, pellagra, lymphatism, alcohol and nicotin, or chronic diseases such as tuberculosis and the cardiopathies affecting young adolescents. The second type of infantilism is that described by Brissaud,[8] who objects to applying the term infantilism to the condition in which the diminutive stature is the principal characteristic, and believes with Meige[9] that the term should be restricted to an anomaly of development in which the morphologic characteristics appertaining to infancy persist beyond the ages at which they should normally be found. The chief characteristic of this second type of infantilism is a myxedema combined with persistence of certain morphologic signs of infancy and failure of normal sex development. Brissaud[8] believed that infantilism in practically all cases is dependent upon insufficiency of the thyroid gland. It may be that this type is the true dysthyreoid, myxedematous form and is to be included among the types of infantilism depending upon primary ductless gland disorders. On the other hand, it is probable too that disease of the thyroid gland is not to be considered the sole cause but that there is disease of two or more of the glands of internal secretion giving rise to the indefinite group lately understood and loosely classified under the term pluriglandular infantilism. Hertoghe[27] and later Ausset[3]

and Breton[7] regarded the various forms of infantilism as expressions of congenital damage to the thyroid gland and thus attempted to reduce all forms of infantilism to a uniform basis. In a consideration of infantilism the conceptions as to what constitutes this condition and what are the factors in its etiology have varied greatly with the different writers. In order to obtain a working rational conception of infantilism it may be helpful to consider in somewhat greater detail the chief features of the condition and then to classify the types according to their distinguishing features and their known or probable etiology.

In the true or so-called dystrophic type of infantilism (Case I, p. 757), defined as cessation of development at the stage of the infant or child, the following findings are characteristic. Such a child has a head which is too large in proportion to the arms and body, much as in the newborn in which there are a strikingly large head, well-developed arms, relatively short legs, small hands and feet and a low position of the umbilicus. Normally, in the first months of life and about to the end of the first year, the lower extremities are much shorter than the trunk. Subsequently there are essentially two periods of growth separated by several years, the first falling between the fifth and seventh years and the second just before puberty, while, with the appearance of puberty, growth has essentially been acquired. In infantilism, furthermore, the genitals and vita sexualis remain partially or entirely undeveloped. The same holds true of the secondary sexual characteristics. There is also a deficient, incomplete involution of the lymphatic apparatus. Growth is retarded. Ossification, as indicated by the appearance of the bone centers and the closure of the epiphyses, is delayed. The childish or infantile measurements of the body tend to persist (Case I, Figs. 145, 146) and the length of the lower extremities remains the same as that of the trunk or may be even less, a characteristic which is not infrequently found. The pelvis, neither masculine nor feminine in type, is infantile, and finally there is also retardation of the psychic development. Such individuals do not show gross defects of intelligence but rather the psyche remains childish.

We know that the period of childhood should be the time for the acquirement of growth and development. This is its principal function. In speaking of infantilism then we mean that the child has failed to acquire this normal growth and development and has preserved, to a more or less degree, the childish form, size and mental development. Peritz[43] would consider only those instances as types of infantilism in which the childish function of growth in length has not been lost but rather has been retarded even to the thirtieth year. In considering the blood-vascular system in the child we find that the blood pressure is lower, the total volume of blood is greater in proportion to body-weight, and the pulse as is well known, is greater, than in the adult. These findings tend also to persist in infantilism.

Besides these distinctions we may now consider the differences in the nervous systems of the child and the adult. In the former there

are probably direct nervous influences exerted upon the heart and the blood-vessels which are not present in the adult. In the child the inhibitory apparatus is still undeveloped but shows its influence at the time of puberty when the pulse becomes slower and approaches the normal rate of the adult. In other words the cerebral nervous influences dominate over the sympathetic in the adult as shown by the development of the inhibitory apparatus. There is, furthermore, in the child, a physiologic hyperirritability which is shown in increased response to stimuli of all kinds and which may evidence itself in intense fright, anxiety, fears, and a sense of dependence. There is also diminished power of concentration. Children are easily diverted, there is a desire to possess everything they see, a tendency to talk, to babble, to spin tales, facts which illustrate the well recognized deficient inhibition. Again there is an increased suggestibility. The nearer the child approaches to puberty the more the inhibitory factors come into prominence and thus one can speak of a conflict, at the time of puberty, between two opposing nervous factors, the sympatheticotrophic contending with the vagotrophic for superiority. As a consequence there are different egos, one the easily excitable and the other the very much suppressed. Many of these characteristics tend to persist beyond the normal periods in instances of infantilism.

Peritz regards the normal development to puberty as intimately related to the maturity of the gonads. In fact, he says one must acknowledge that this sexual maturity is the deciding influence at this time. The further this maturity is delayed the longer these individuals remain children and in those cases where sexual maturity is never acquired these individuals remain infantile for the remainder of their lives. Peritz[43] believes that herein lies the basic problem of the whole subject of infantilism, and the various forms of which differentiate themselves into groups characterized by a primary or secondary underdevelopment or absence of sexual maturity. In the one case we are concerned with an infantilism exhibiting primary in the other secondary dysgenitalism. Accordingly, in considering infantilism, we should be on the watch not merely for evidences of external childish configuration but should also note the degree of mental development attained and, because of its very great secondary influence, the degree of development of the sex-gland function. In brief Peritz and others would regard infantilism not as dependent upon the sex-gland function directly but as secondarily very greatly influenced by it. In fact he would divide infantilism into two large groups depending upon whether the function of the sex glands is primarily or secondarily inhibited.

Falta,[18] on the other hand, attempts to determine the position of the ductless glands generally in the pathogenesis of infantilism. If the latter is characterized by a general cessation of growth of the entire organism at the stage of the child, then the gonads must simultaneously be involved and fail to develop. Up to the present the peculiar rôle of the gonads in the ductless-gland system has not been sufficiently taken into account. They do not attain full maturity until puberty

and thus insure the normal progressive development of the organism even though they functionate from earliest childhood, whereas the other ductless glands are already fully developed in the newborn. Thus the normally and relatively late development of the gonads necessarily becomes a subordinate influence in the whole disease syndrome of infantilism for we never find in infantilism those very fundamental developmental disturbances as seen in eunuchoidism in which there is complete absence of sex function. The genitalia in infantilism appear and function like those of a child whereas in the eunuchoids gonadal function is entirely or practically entirely absent. Thus we see that the infantile sex glands and genitalia are very different from those of the eunuchoids. If, as Falta would believe, pure infantilism is caused by a cessation of growth in the whole organism at the stage of the child then the ductless glands, as well as the skeleton, the hematopoietic apparatus, and the central nervous system, also remain childish and thus we can understand how the developmental *retardation of the ductless glands is merely coördinated with and not responsible for the retardation in growth of the whole organism.* As a consequence, if these premises are correct, one cannot regard infantilism as a primary ductless gland disease. It seems to Falta no longer justified to apply the term infantilism to a sharply defined disease syndrome which is dependent upon primary disease or developmental disturbance of a single ductless gland such as childish myxedema or juvenile hypophyseal dystrophy or eunuchoidism. In other words, Falta would reserve the term infantilism for a *general retardation of development of the entire organism,* including the ductless glands with the body and mind, and would regard the sexual under-development merely as a subordinate factor in the clinical syndrome inasmuch as infantilism has not been developed because of but rather in coördination with under-development and under-function of the sex glands.

More recently great interest has been aroused in the study and understanding of infantilism particularly since the glands of internal secretion have received so much attention and since their influence upon the development of the entire organism, mind as well as body, has been recognized. The term vegetative disturbances, which is in more or less common usage, includes in its broad sense every form of developmental retardation. Since it has become known that the growth and normal development of the organism is accomplished only by the normal development of the ductless-gland system, many recent investigations have been directed in an endeavor to find, in the anomalies of the ductless glands, the causes of the various vegetative disturbances. We find accordingly a group of the latter which is clearly dependent upon diseases of one or more of the ductless glands. Then again there is a second group of developmental anomalies whose etiology is not so certainly to be found in the ductless glands or is only in part located there, and again there is a third large group in which demonstrable disturbances and changes in the ductless glands have not been observed. In this latter group Falta places true or dystrophic

infantilism, true dwarfism, chondrodystrophy, rachitic dwarfism and mongolianism. Accordingly we may group these vegetative or developmental disturbances into two large well-defined classes, namely, the one the pure or dystrophic class or type and the other depending upon demonstrable disturbances and changes in the ductless glands. There is a question whether one should class under infantilism the pure types of the first group, as some authors would probably do, or whether to regard infantilism, in its broad sense, as depending also upon disease of the ductless glands. In this presentation of the subject I shall speak first of true, dystrophic types of infantilism and secondly of those types in which primary disease of the ductless glands is a certain etiologic factor. It is possible, indeed probable, that with our increasing knowledge concerning the ductless glands, types of the first group now regarded as pure dystrophic infantilism will prove to be secondary to ductless-gland disease of one or more members just as in the past pure types of ductless-gland dystrophy have been recognized and separated from the numerous cases of ill-defined infantilism.

I should like now to speak in more detail of this second large subdivision of infantilism depending upon diseases of the glands of internal secretion. Whether these types should be regarded as true infantilism or not is a matter still open for discussion and for difference of opinion. However, at the present time for the sake of completeness and because of the many points of similarity between the true dystrophic types and those dependent upon ductless-gland disorders, I shall consider briefly types of infantilism or perhaps better pseudo-infantilism caused by disorders in the internal secretions.

It may be that when our knowledge of certain of the ductless glands is greater and more precise the types which we now include under so-called true dystrophic infantilism will be found to be the result of disease of one or more of these glands. Thus we now recognize very definite types of developmental disturbance depending upon disease or disorders of the thyroid, hypophysis and the sex glands. Disorders of the adrenal, of the thymus and pancreas are less well understood and consequently the types of corporeal change if any depending upon these disorders are not so clearly recognized. There is another type which has been called by many "pluriglandular disease" by which is meant that there are evidences of disease of several of the glands and that it is impossible to recognize which of these glands is primarily responsible, if indeed any of the glands is more affected than the other, and finally we must consider the group of cases which have been classed under "partial infantilism" and which are characterized by failure of development or atrophy of particular portions or systems of the organism. Thus, for example, we have cases of aplasia or atrophy of the sex glands without other outspoken signs of infantilism; cases of deficiency in the realm of the cardiovascular system; infantilism characterized by persistence of the childish character of voice, with the failure of development of the adult characteristics of voice and voice-forming organs; failure of hair growth with good corporeal proportions

and cases of possibly pure "psychic infantilism" without corporeal infantilism, such as a case described by Peritz resulting from primary brain lesion and without corporeal infantilism. These cases have also been described by Anton.

As stated above I shall in this review regard as cases of pure infantilism the types described by Falta, Peritz and others, but on account of the many points of resemblance with the ductless-gland developmental disturbances I shall consider briefly those types of failure of normal development at puberty depending upon anomalies of the ductless glands and finally shall mention three groups which similarly have many points of resemblance with pure infantilism and which are classed under "partial infantilism." This subdivision of the large subject of infantilism is given for the sake of completeness and convenience rather than because of any hard and fast classification upon the basis of etiology.

II. DYSTROPHIC TRUE INFANTILISM

Characteristics.—A very definite, readily recognized type of infantilism which we might regard as the true, dystrophic type is that first described by Lorain. It is characterized by a very considerable disturbance of growth and a definitely diminished size of the body as compared with the normal. The figure resembles that of a child and there is in addition a definite under-development of the psyche giving rise to the condition sometimes called "psychic infantilism." The skeleton retains the childish measurements, that is, the length of the lower extremities is less than that of the upper trunk or exceeds it only very slightly. The head is relatively large (Case I, Fig. 146), bones are gracile, the umbilicus is low and the pelvis is neither masculine nor feminine in type but, on the contrary, infantile. The appearance of the ossification centers, the dental development and the closure of the epiphyses are delayed (Case I, Fig. 147). The genitalia remain under-developed and resemble in size and form those of a child. Genital function is not entirely absent but rather corresponds to that of a child and consequently we find the secondary sex characters poorly developed or altogether absent. The vita sexualis is also childish. There is usually a good growth of scalp hair, but a lack of hair on the trunk, in the pubic and perineal regions as also in the axillæ. There is a deficient involution of the lymphatic apparatus and a relatively high lymphocyte count. There need be no outspoken status lymphaticus although it is probable that the damage, which causes the infantilism, may also be responsible for status lymphaticus. Similarly the anemia which is not infrequently found in infantilism may be regarded as a direct result of the action of toxins or other injurious factors. The internal organs are mostly normal, while the vascular system in most cases shows a mild grade of hypoplasia. The blood pressure is frequently at the lower limit of normal. According to Falta, determinations of the respiratory exchange apparently have not been made, and the carbohydrate tolerance corresponded, in those cases

which he examined, to very nearly the normal. Functional tests of the vegetative nervous system showed meanwhile a slight diminution of irritability though this statement probably deserves confirmation. In true infantilism it is furthermore characteristic to have a persistence of the childish features. We find also a childish logic, childish tendencies to imitate and a certain anxiety, apprehension and dependence. The childish expressions of deficient inhibition, which

FIG. 145.—Case I. Photograph of the patient, the little girl, five years and two months of age, her younger brother one year and nine months of age, and their tall father. Note the severe form of true dystrophic infantilism represented by the little girl at the age of five years and two months as compared with her normal younger brother of only one year and nine months of age. The causative injurious factor producing the infantilism was of intra-uterine origin, but of unknown etiology.

normally disappear as puberty is approached, tend to persist in infantilism. Thus we see the diminished power of concentration, the desire to possess everything the eye sees, the tendency to talk, babble, spin tales, and the abnormal suggestibility.

CASE I (FIGS. 145–149)

G. K. (Harriet Lane Home Dispensary. No. 14909. Johns Hopkins Hospital.) A type of true dystrophic infantilism of unknown etiology. Special findings are pyelocystitis, pyelonephritis, tetany, acidosis, congenital dislocation of the hip.

Admitted July 20, 1917. G. K., female, age four years and nine months.

Complaint.—Polyuria, polydypsia, frequency of micturition for the past two to three years, poor appetite, itchings of arms and hands.

Family History.—The father and mother are living and well, the former is 32 and of tall stature, and the latter is 36 years of age and of medium stature. One brother is living and well, 16 months old. There are seven step-brothers and sisters living and well, one dead. The family history is negative for tuberculosis, alcholism, or syphilis.

Past History.—Birth was normal. She was breast fed for two months and then put on artificial feeding, which was frequently changed because the child did not thrive. When she was two years of age she was said to have had "milk poisoning" and was given orange juice. A plaster cast was applied to the left leg for a period of six months for some apparent trouble in the hip or leg. Six months ago the

Fig. 146.—Case I. Photograph of patient and her younger brother; same as in Fig. 145.

child was unable to walk because of pain in the feet. At this same time the urine was examined and the child was said by the attending physician to have diabetes.

Physicial Examination.—The child is very small and definitely undersized but appears to have good mental development. Temperature is 99 degrees. Weight 21½ lbs. Length, 79.8 cm.; circumference of head, 45 cm.; circumference of chest, 46.8 cm. General examination of the head and chest reveals nothing abnormal. Abdominal examination is negative except for the fact that the bladder can be palpated at the level of one-third the distance between the symphysis and the umbilicus. Urine is cloudy; specific gravity, 1005; albumin present; many pus cells and an occasional cast are found. On July 16, two days after admission to dispensary, another examination was made of the urine, which again showed large quantities of albumin and pus with an occasional cast. Patient was given sodium bicarbonate and was slightly improved. On July 20, child was brought to the hospital on account of the following conditions: During the afternoon she was suddenly seized with pain in her hands and feet. Mother noticed that the child's feet were rigid and held strongly flexed and that the hands also were rigid and

FIG. 147.—Case I. *X*-ray of hands, showing diminutive size of phalanges and delayed appearance of ossification centers in the carpus and wide-open epiphyses.

FIG. 148.—Case I. *X*-ray of jaw to show the dentition which is not much delayed or disturbed in this instance.

flexed at the wrist. The child was wholly conscious. In brief, there was a typical carpo-pedal spasm, such as is seen in tetany.

On July 20, 1917, patient was admitted to the Harriet Lane Home, where she remained until Sept. 5, 1917, since which time frequent visits have been made in order to observe the child's further condition.

Examination (continued) July 20, 1917. Child is extremely small for her age but well developed, has a good color and is well nourished, intelligent and entirely conscious. She is in no apparent pain. The most striking finding is the way she holds her hands and feet. The arms are bent at the elbows and the hands are

Fig. 149.—Case I. *X*-ray of skull, which is of good size and shows no gross abnormalities. It is fairly large as compared with the size of the body of Figs. 145, 146.

strongly flexed and held against her neck on either side. The fingers are held straight and the thumb is bent across the palm of the hand. Feet are forcibly extended.

Skin.—Smooth. No cutaneous lesions. Erythema over both legs, present since onset of spasm. A small scar is seen over lumbar spines, the result of an old injury.

Head.—Well formed, symmetrical.

Eyes.—Pupils equal, react normally; scleræ clear.

Mouth.—Twenty teeth, fairly well kept. Tongue not coated. Pharynx contains some adenoid tissue. No exudate or inflammation.

Glands.—No general glandular enlargement.

Chest.—Well formed. Respirations regular. Lungs and heart negative.

Abdomen.—Rather full; walls tense; liver not enlarged; spleen not felt.

Genitalia.—Normal. No discharge. Slight redness.

Extremities.—Hands and feet painful when moved passively. Child will not move her toes or fingers spontaneously on account of pain. There is no limitation of motion in the arms.

Reflexes.—Left knee jerk more active than right, but both can be obtained. Chvostek not obtained.

W. B. C., 13,400. Vaginal smear, negative. Urine: Alkaline, clear, light-yellow; specific gravity, 1005; albumen +; acetone + (trace); no pus cells; no sugar. Calcium chlorid, gr. xv, given every four hours.

July 21, 1917. After 60 gr. of calcium chlorid had been given there was no carpo-pedal spasm and the child was comfortable. No Chvostek. Trousseau present.

July 23, 1917. Urine (24 hour specimen): Acid, pale-yellow, cloudy; amount 1729 c.c.; specific gravity, 1007; albumen +++; acetone 0; sugar 0; many pus cells. Urotropin and calcium chlorid discontinued. Very marked hyperpnea, very drowsy, rather fretful.

Urine, separate specimens:

1 p.m.	Acid, acetone trace, albumen +	, sugar 0, pus ++
2 p.m.	Acid, acetone trace, albumen +	, sugar 0, pus ++
4 p.m.	Acid, acetone trace, albumen +++	, sugar 0, pus ++
8 p.m.	Acid, acetone trace, albumen +++	, sugar 0, pus ++
11 p.m.	Acid, acetone trace, albumen ++	, sugar 0, pus ++

At 11 p.m., child sleeping quietly, hyperpnea very much reduced. Given glucose, gm. xii, and cane sugar, gm. xii, at 6 p.m.

July 27, 1917. Pthalein excretion:

First hour	2 per cent.
Second hour	6 per cent.
Third and fourth	16 per cent.
Total in four hours	24 per cent.

Between Aug. 8, 1917, and Dec. 5, 1917, the child was under observation from time to time. There was a gradual slight improvement and the general appearance was good. Sodium bicarbonate treatment was continued, although on examination the urine continued to contain large numbers of leukocytes and also some red blood-cells and a heavy cloud of albumen. No casts were seen. During this time temperature was normal most of the time, occasionally rising to 99 or 99.8 degrees. There was still frequent micturition, particularly at night, and the child would awaken and ask for water two and three times during the night. There was great thirst. Bowels tended to be constipated and the child complained of itching of the hands, which on examination were seen to be cyanotic.

Measurements made Dec. 13, 1917:

	Centimeters
Circumference of head	46.0
Circumference of chest, level of nipples	49.0
Circumference of abdomen, 3 cm. above umbilicus	47.5
Circumference of pelvis, level of trochanters	44.5
Distance between anterior superior spines	14.5
Circumference of right thigh, level of perineum	24.5
Circumference of right calf	16.2
Circumference of left thigh, level of perineum	23.2
Circumference of left calf	16.0
Span of arms, to tip of middle fingers	83.5
Right arm, acromion to tip of middle finger	36.0
Left arm, acromion to tip of middle finger	35.0

	Centimeters
Right leg, anterior sup. spine to int. malleolus	39.0
Left leg, anterior sup. spine to int. malleolus	36.5
Apparent shortening, left leg	2.0
Right foot	13.0
Left foot	12.5
Hand, glove measurement, right	10.5
Hand, glove measurement, left	10.5

Further Examination, Dec. 13, 1917.—The general appearance is not striking, aside from the very small body and fairly small head. No gross abnormalities are made out. Patient is quite well formed as to general figure. As she walks the left foot is slightly everted and there is a kind of limp with a delayed use of the left leg. She also uses the left arm less than the right.

The abdomen is not especially protuberant. There is no spinal curvature. Facial features are good, symmetrical, and small. There is no evidence of cretinism. No facial asymmetry as child grimaces. She is moderately well nourished and cheeks and mucous membranes are of good color. Skin is pink, thin, delicate, and moderately dry; not in any way coarse or edematous. The complexion is fair. Child understands readily, answers questions and looks bright. She has a good set of first teeth, which are all erupted. There is a good growth of fine black scalp hair. Eyebrows and eyelashes well grown. There is no dulness under the manubrium. The tongue is slightly coated and small. There is a moderate amount of adenoid tissue in the pharynx; tonsils are small but ragged and with large crypts. There is no spasticity nor flaccidity of the arms and legs. The muscular tone is about the same on the two sides.

Reflexes.—Knee jerks moderately active. Plantar reflex is normal on the two sides, though the response is slow.

Orthopedic Consultation.—The child was referred to the orthopedic department because of a congenital dislocation of the left hip which was discovered in the first instance by *x*-ray examination, made primarily for study of the kidneys. Spine was found to be normal. The extremities were negative on examination except for the left leg. Patient walked with a limp on the left side and the gait was wabbly in character because of lack of fixation on this side. The left leg appeared shorter than the right. There was an absence of resistance, on palpation, over the normal position of the head of the femur. Upon traction and release it was found that the femur could be moved quite freely, as in cases of congenital dislocation of the head of the femur. Trendelenburg sign was positive.

Measurements:

	Centimeters
Bryant's line, right	3.5
Bryant's line, left	1.0
Great trochanter to ext. malleolus, right	35.0
Great trochanter to ext. malleolus, left	35.5
Ant. sup. spine to external malleolus, right	38.0
Ant. sup. spine to external malleolus, left	36.0

Diagnosis.—Congenital dislocation of the left hip with anteversion of the neck. The head of the femur is in its normal position on the right but is missing on the left in the position of the acetabulum. The trochanter is elevated on the left and the head of the femur can be felt posteriorly above the acetabulum. *X*-ray picture suggests an anteverted neck.

Dec. 20, 1917. Left congenital dislocation of the hip was reduced and a plaster cast applied.

On Dec. 21, albumen and a trace of acetone were still present in the urine.

Dec. 30, 1917. *On Discharge:* Patient has been walking about for the past week. It is unnecessary to add an addition to the left heel as patient walked quite well. *X*-ray showed dislocation reduced.

In the middle of January, 1918, while patient was at a local children's hospital school, the left hip was again dislocated. Several days later patient was given ether for about 15 minutes; the hip was reduced and a plaster cast reapplied. She seemed to be doing well for several days when suddenly there was a great diminution in the quantity of urine passed. Following this suppression there were frequent short convulsions involving the face and arms and lasting about one hour. There was an odor of acetone in her breath, and hyperpnea was present.

Jan. 25, 1918. Patient was rather drowsy, falling asleep very easily. When aroused was clear mentally. Appeared sick. Cheeks flushed. She was irritable. She lost weight as compared with her condition two months ago. There was an odor of acetone to the breath.

During the examination patient had at times very marked tremor of both arms and hands, but no convulsions. W. B. C., 22,200. Urine: Specific gravity, 1010; albumen +++; sugar 0; acetone, trace; diacetic 0; guaiac +; many red and white blood-cells present. No casts seen.

The child was given sodium bicarbonate, gr. xx, every two hours, together with lemonade containing cane sugar and glucose, 12.5 gr. of each to every 200 c.c. Under this treatment the child rapidly gained. The quantity of urine voided also increased very definitely and hyperpnea soon disappeared. Toward the end of January the urine still contained a large amount of pus. Frequent micturition with considerable pain was present. By Feb. 2, 1918, the child had improved considerably and was sent back to the hospital school.

Discussion.—The patient whose history and examination are given above illustrates a type of general dystrophic infantilism, the precise etiology of which is not revealed either in the history or in the physical examination. There is a strikingly greater physical retardation than mental. In fact the mental development seems to have been but slightly impaired. There is a diminutive stature of normal proportions. This is well shown by the measurements of the body and by comparison with the patient's younger brother. In spite of the considerable discrepancy in their ages, the patient at five years and nine months of age is of slighter build and only slightly taller than her brother at two years and four months, a fact which is readily recognized by reference to Figs. 145, 146. Attention is directed to Figs. 145, 146 showing the father with the patient and the younger son; Fig. 147 showing the *x*-ray of the hand and wrist; Fig. 148 showing the jaw with the unerupted molars, a practically normal dentition; and Fig. 149 showing the *x*-ray of the skull with normal sella turcica. Incidental complications in the case of considerable interest are the congenital dislocation of the left hip, the tendency to tetany, the pyelonephritis, and the acidosis, factors which are in great part to be looked upon as effects and not causes of the infantilism.

Di Gaspero[23] emphasizes particularly the importance of the childish conception of value and the childish suggestibility. The pitch and modulation of the voice are similarly childish. There is an absence of the childish playfulness and levity and instead there are often feelings of insufficiency, reserve and shyness. The attention is easily gotten, is prompt, but is very easily distracted. Complicated mental impressions awaken a feeling of aversion. These psychic characteristics are very different from those found in the eunuchoids. These children thus stand corporeally and psychically two to three years behind the children of their own age and the older they become the greater the difference between them and normal individuals.

Forms.—Various forms or subvarieties of infantilism may be produced according to the intensity of action of the causative factor and according to the age at which the influence of this factor has exerted itself; thus we have the striking form in which these children

remain both corporeally and psychically absolutely infantile in their development and remain so throughout their lives. On the other hand, there may be the very mild types often recognized and called "formes frustes." If the causative injurious factor producing the infantilism has been present in infancy or even *in utero* the more severe forms, of infantilism (Figs. 145, 146, Case I, p. 757) are produced, one type of which may possibly be the striking hypoplastic dwarfism described by Breus Kolisko and cited by Falta. On the other hand, if the causative factor appears relatively late, a form which has been called "juvenile" results. In this type the skeleton is not so purely childish in its type and the genitals are relatively well developed. Similarly there may be juvenile forms of psychic infantilism. Then again depending upon whether the psyche, the skeleton or the genitalia are alone or more particularly affected we may have types of so-called partial infantilism to be described in a later chapter.

Etiology.—A great variety of causative factors are recognized in the production of true infantilism. In the first place we may mention various injurious factors of toxic and infectious origin, affecting the child not only directly but also in an hereditary way by having acted injuriously upon one or both parents. As examples, we may mention the toxins of such chronic diseases as syphilis, tuberculosis, pellagra, malaria, and the injurious results of alcoholism in the parents. At other times the children themselves may have been directly attacked by severe infectious diseases with a resultant combination of corporeal and psychic infantilism. Early chronic heart disease may have a similar result as also typhus and certain cerebral injuries. There are further definite types of infantilism following upon the injurious influence of bad hygienic surroundings and deficient nutrition; of chronic diarrhea and of hydrocephalus. The latter may possibly be included under the types produced by pituitary deficiency. Disease of the pancreas or disturbance of its function has been described as a causative factor leading to the so-called pancreatic infantilism. Severe disease of the liver is said similarly to lead to infantilism as, for example, in a case of hypertrophic biliary cirrhosis described by Lereboullet. Then again Peritz has given status thymicolymphaticus as a cause, and by others cardio-vascular aplasia and primary disease of the brain, unilateral or bilateral, have been given as etiologic factors. The severity of the type of infantilism depends upon the intensity of action of these causative factors and also as already stated upon the age at which the causative factor exerts its influence upon the organism. Further discussion of the various types of infantilism depending upon these different causative factors will be considered below. Then again the causative factor may be quite obscure (Case I, Fig. 145).

The clearest type of infantilism resulting from damage produced by toxins or infections is probably that represented by inherited syphilis. It should not be forgotten however that early acquired syphilis may act injuriously in the same manner as congenital syphilis. The syphilitic form is rather easily recognized as contrasted with other

forms of dystrophic infantilism, the result of infectious diseases, for in this latter type we have to rely more upon history and general impressions. In the syphilitic form, however, the Wassermann reaction, which is always positive, is a great help in the diagnosis. The diagnosis rests upon the triad of symptoms so frequently pointed out, namely, the fissures around the orifices of the body, the parenchymatous keratitis and the Hutchinsonian teeth. In the early acquired disease these signs are also present. In what manner the syphilitic poison acts as a cause of infantile development is difficult to say. Whether furthermore there is a parallelism in the severity of infantilism with the severity of the infection it is similarly impossible to say. There is an impression, however, that in the forms of syphilis in which there are no severe local signs or symptoms infantilism is prone to develop. This is somewhat similar to the frequency of tabes in cases of syphilis without severe local symptoms and therefore receiving little attention. The combination of infantile tabes with infantilism is fairly common. There is an interesting frequency of epilepsy developing upon general disease of the central nervous system of syphilitic nature and combined with infantilism. It may be, as Peritz believes, that infantilism results in some manner as a consequence of disease of the central nervous system. According to Peritz, further, the processes by which the chronic infections lead to infantilism are the same whether the latter is produced through injury to the sex glands or through direct injury to the organism generally. This he thinks is brought about by the fact that the infectious diseases all produce a lipoid-binding toxin, as shown, for example, in tuberculosis by the work of Calmette[10] and Petit,[44] which toxin produces results very similar to those caused by alcoholism in the parents or in early childhood. Again there is the parallelism, according to the work of Meyer and Overton, in the case of alcohol which is primarily a lipoid poison. Thus Meyer regards the action of alcohol as an acute protoplasmic poison which destroys the equilibrium in the cell and has the property of dissolving the lipoids. It is thus possible that abnormal processes are developed within the cell and that this disturbance may be produced in certain organs or in particular groups of cells such as the sex cells in which case the damage may be general or limited to the egg itself at or before its fertilization.

A *second* group of true infantilism cases includes those resulting from early acquired diseases such as tuberculosis, typhoid, pellagra, chronic heart disease and malaria. As an example of this group we may mention infantilism which results from congenital or early acquired heart disease, and which represents possibly the purest form of dystrophic infantilism. In this form we are not dealing with a question of toxins produced by disease but are concerned rather with the results of a general malnutrition caused by deficient distribution of blood to the organs and to the periphery. Thus Peritz[43] illustrates and describes the case of a boy of 16 who is very much under-developed and whose hand shows widely open epiphyses. This under-develop-

ment he regards as the result of old and early acquired heart disease. Krause showed that in cases of this kind the peripheral blood had a very definitely increased venous character as a result of the deficient heart action. The circulation as a consequence suffers. There is deficient oxygenation in the various organs which interferes with their normal function and is thus responsible for the failure of growth in the young organism. It is naturally to be remembered that there may be other causes for the developmental disturbance in these cases of congenital heart disease, for such patients are frequently the victims of tuberculosis which may be an important contributing factor. Thus, for example: v. Recklinghausen described the case of a woman 25 years of age who showed a completely infantile habitus and who died of tuberculosis after a second childbirth.

There is a *third group* of cases of infantilism the etiology of which seems doubtless to be sought in the influence of bad hygienic surroundings and deficient nutrition (Fig. 145, Case I, p. 757). Examples of these cases are to be found in various children's clinics and orphan asylums. A similar type of infantilism which is attributable to chronic intestinal infection is in all probability that described by C. A. Herter.[26] Toxic products absorbed from the intestinal canal are responsible here, in a way which is possibly very similar to the inhibition of growth but not of weight in young rats fed with isolated proteins as reported by Osborne and Mendel.[35]

A *fourth group* may be regarded as resulting from nutritional disturbances existing since early infancy or childhood and expressing themselves in states of chronic diarrhea, of pancreatic insufficiency and of severe extensive disease of the liver. It is probable that in these cases the infantilism is caused by the disturbances in nutrition, for, with the improvement in the latter, growth can again be stimulated and may result in a practically normal development. Thus in those cases of infantilism with diarrhea and fatty stools which have been described by Bramwell and later Rentoul (Falta)[18] it is probable that pancreatic disturbance was the primary cause for, following the administration of pancreatin, the stools became normal and there was a rapid increase in body-weight. It seems probable that these cases are not the result of a disordered internal secretion of the pancreas but rather, as stated above, the result of digestive disturbance produced by abnormal pancreatic function. I shall return to a discussion of so-called pancreatic infantilism under diseases of the ductless gland. It is probable that diseases of the liver such as hypertrophic biliary cirrhosis act in a similar manner.

A *fifth large* subdivision of cases of infantilism are those which are grouped under the indefinite term of status thymicolymphaticus. It is a question whether these are cases of true infantilism. Peritz is inclined to regard them as cases of true dystrophic infantilism and is inclined to emphasize this group in his discussion of the subject. Paltauf[39] first described the condition of status thymicolymphaticus. The individual afflicted has a pale, anemic, pasty appearance, and is

inclined somewhat to adiposity, showing itself in a well developed panniculus adiposus. The lymph glands are hyperplastic and frequently there is retromanubrial dulness demonstrable by percussion and due in all probability to a persistent thymus. The pharyngeal and tonsillar lymphoid tissue is abundant; there is a narrowing of the arterial system particularly of the aorta, such as Virchow described as a sign of chlorosis. In the female there may be an under-development of the whole genital apparatus. There may be stenosis of the vagina and the uterus is very small, whereas the ovaries are unusually large, smooth and in older women may be cystic. In the male the testes are sometimes normal but frequently show an increase in connective tissue. There may be testicular atrophy and spermatogenesis often disappears. The beard is poorly developed and pubic and axillary hair are scant. The psyche is also infantile which shows itself in absent or late sexual perception, and the menses may be retarded and make their first appearance at the nineteenth year. In males there is an absence of spermatogenic secretion. Corporeally these individuals do not follow the characteristic law of the subnormal stature in infantilism, for they are often very much over the normal, a few are of the average and still fewer are less than the average size. Thus in status thymicolymphaticus the type of infantilism is not always nor only of the true corporeal kind. There is frequently a psychic infantilism as well showing itself in anxiety, apprehension, dependence, drowsiness and a lack of general ability. Patients thus afflicted concentrate badly, learn slowly, and have a restless sleep. In some cases the outward signs of lymphatism are not apparent but there is usually a characteristic body and psyche, retardation of development together with striking increase in pharyngeal and tonsillar lymphatic tissue. In cases of this kind there is often great improvement after adenoidectomy and tonsillectomy. There are, on the other hand, individuals in whom the genital aplasia is the most striking feature. In many instances one can recognize a chlorotic condition associated with signs of an aplastic vascular system. These cases should perhaps not be classified under status thymicolymphaticus. On the other hand, they should not be confused with those cases of myxedematous nature in whom the signs of thyroid insufficiency are not very definite, the so-called "formes frustes." It may be that the syndrome of status thymicolymphaticus in these cases is the result of a primary thyroid disturbance rather than the cause of the underdevelopment and the myxedematous appearance. It should be mentioned that individuals suffering from status thymicolymphaticus in whom tonsillar enlargement and diseases are common are poor operative risks. It is in these patients that sudden death, the so-called thymic death, may follow a brief chloroform or ether narcosis preliminary to a simple tonsillectomy.

In recent years a great deal of experimental investigation has been directed to the thymus gland. It may be well to consider the evidence we have for believing that the thymus is or is not of itself responsible for

the condition of status thymicolymphaticus and for general constitutional disturbances. Furthermore, the much discussed relationship between the thymus and the sex glands deserves consideration. Clinical data seem to indicate that in dysgenitalism in the human as also in eunuchoids there is a persistent thymus, and experiments seem to show that in castrated animals the thymus is larger than in the control animals. The reverse seems also to hold, thus according to Soli after removal of the thymus the testes lose considerably in weight. He saw no change in the other glands, the spleen, suprarenal, thyroid and the hypophysis. On the other hand, the secondary sex characters in these animals are less well developed than in the control animals. There are differences of opinion as to whether the disturbances which one finds in status thymicolymphaticus are due primarily to hypertrophy of the thymus, as Grawitz[25] believes, or whether according to Paltauf they are dependent upon the general hyperplasia of the lymph apparatus, in which the thymus hypertrophy is merely a participant. More recently Basch[5] and Klose and Vogt[32] have studied the disturbances arising in thymectomized animals. Basch reports bony changes occurring in thymectomized dogs. In the second and third week after extirpation of the thymus the bones are more gracile, less compact and bend more easily than those of the control animals. The calcium excretion is increased and in case of fracture of the bones there is a deficient callus formation. Basch believes further that there is a decreased psychic activity and lowered intelligence in the animals. In a very extensive report Klose and Vogt[32] described the changes after thymectomy in animals in which the thymus extirpation was done 10 days after birth at the time when the thymus is supposed to be most active. Klose distinguishes three stages, the first stage characterized by adiposity, such as has been described in children the victims of lymphatism. In the second stage there is a loss of weight in the animals. There is also a retardation of growth; they are less active and awkward in their movements; there are muscular spasms and often spontaneous fracture occurs. In the third stage there is a definite psychic disturbance in which an almost complete mental deficiency occurs and eventually the animals die in coma thymicum.

It is questionable whether all of these signs and symptoms described by Basch and Klose and Vogt in thymectomized animals are to be referred to the extirpation of the thymus itself. Pepère[41] points out that in many mammals accessory parathyroids are found in the thymus and that thus symptoms of tetany and increased calcium excretion after thymectomy may be due to parathyroid removal. The work of Park and McClure[40] throws a great deal of light upon these experiments and particularly upon the function of the thymus. They conclude from a very careful and extensive investigation on the effects of thymus extirpation in the dog that the thymus gland is not essential to life; that its extirpation is not followed by any pathologic skeletal changes, such as rickets, and is not productive of any detectable alterations in the hair, teeth, contour of the body, muscular development, strength,

activity or intelligence of the experimental animals. They feel furthermore that the extirpation of the thymus does not influence growth or development to any definite degree, and probably produces no alterations in the organs of internal secretion. The results of this work throw a considerable doubt upon the changes which are stated to follow thymectomy by Basch and Klose and Vogt and make it seem very improbable indeed that the thymus is or could be primarily responsible for a condition of true infantilism. Thus we see that the relation between status thymicolymphaticus and infantilism is still very obscure. Peritz would regard the whole condition as a secondary dysgenitalism and the disturbances seen in this form of infantilism as results of diminished or absent function of the sex glands.

Bartel,[4] on the other hand, believes there is a disturbance of the entire trophic nature of the whole organism as the result is a congenitally hypoplastic constitution. This of course does not throw any more light on the relation of status thymicolymphaticus to infantilism. He believes that the so-called hypoplastic constitution may in one instance result in the development of latent tuberculosis, in another in infantilism, and finally into a large number of vague disturbances in which the angio-neurotic-chlorotic symptoms predominate, these various results depending upon the principal site of injury and the severity of the condition. It still remains doubtful whether the type of infantilism described thus by Bartel[4] is to be regarded as a result of status thymicolymphaticus or as the result of disturbance of secretion in the ductless gland or whether perhaps it represents a transition form between the true dystrophic infantilism and the associated disturbances in the realm of the ductless glands. The fact that a pure status thymicolymphaticus does not lead to true infantilism indicates that a persistent thymus and lymphatism generally are not the primary causes but that in many cases there is a general dystrophy which of itself leads to infantilism with signs of lymphatism.

Another form of true infantilism is that seen in those cases which result from cardio-vascular aplasia, the so-called angioplastic types and in those following upon primary disease of the brain whether this be unilateral or bilateral.

III. INFANTILISM ON THE BASIS OF DISEASE OF THE GLANDS OF INTERNAL SECRETION

As stated above, on account of the many points of similarity between true infantilism and those types of developmental retardation resulting from ductless-gland disease and also for aid in differential diagnosis it is thought advantageous to include in this section of the review brief accounts of infantilism types which are recognized today as depending primarily upon disease of one of the ductless glands and exhibiting secondary manifestations resulting from diseases in other glands.

Since the principal functions of the fetus and developing child are growth and cellular hyperplasia of the various systems and organs and

since we know that the importance of certain if not all of the ductless glands such as the thymus and thyroid is far greater to the growing organism than to the adult it is readily understood that any influence which might injure the normal function of the glands would have greater detrimental effect than in the adult organism which had attained its growth. Again the correlation between these glands and the different systems in the growing child is closer and far more active than in the adult, a fact which has been abundantly proved by evidence obtained from experiments on young animals as compared with similar experiments on adult animals. As a good example of this may be mentioned the fact that experimental pituitary deficiency exerts a far greater inhibitive influence upon the development of the sexual system in young animals than in adults who have attained normal development. As a consequence we have to reckon in the young organism with additional and secondary developmental effects produced by a retarded sexual maturity. Thus in the growing organism it is important to have a proper function of every gland and organ in order to avoid interference in the orderly progressive differential development of every tissue in the body including such as the nervous, osseous and glandular systems. One of the glands whose proper function is of the greatest importance to the fetus and the growing child is the thyroid.

1. Thyroid. Dysthyreogenous Infantilism.—(Case II, Figs. 150–155). A brief account of the forms of infantilism depending upon disease of the thyroid gland or disturbance in its function will be given here. (For a fuller account the reader is referred to Chapter LXXXII, section on the thyroid, page 680.) Absence of the thyroid or of its secretion leads to dwarfism (Case II, Fig. 150) one of the most striking types of dysthyreogenous infantilism. This condition is characterized by disturbance in ossification as is shown by the excessive retardation of development in the ossification ecnters, by delayed closure of the epiphyses (Case II, Figs. 154, 155) and further by disturbances of development in the bone marrow. The bone formation, so far as it has taken place, is however of abnormal density. There are, furthermore, disturbances in dentition (Case II, Fig. 152) and in the development of the central nervous system in which the mental development particularly suffers. There are also the characteristic myxedematous skin changes and disturbances in the development of the genital apparatus leading to the added element of dysgenitalism. It is probable that, though the primary and essential feature of the disease is the absence or diminution of the thyroid secretion, there are added secondary features dependent upon disturbance in function in the remainder of the ductless glands.

The second form of dysthyreogenous infantilism is that known by the term of "endemic cretinism" and "myxedema." This condition is not only dependent upon "goiterous" degeneration of the thyroid gland but it is very probable that the damaging factors in cretinism influence directly the central nervous system and the other ductless

glands, such as the hypophysis, (Case II, Fig. 151) and thus cause the manifold and variable characteristics seen. Such cretinic individuals remain very definitely retarded in growth. The disturbances are not necessarily proportionate; thus ossification may in one instance be principally affected, in another the developmental disturbances of the central nervous system may be predominant. Sometimes the retardation of growth is most noticeable and in other instances the

FIG. 150.—Case II. Photographs of patient taken May 17, 1917. Age thirteen. Height 135.0 cm. Note general corporeal symmetry; the characteristic facial expression, with depressed bridge of nose. An example of dysthyreogenous infantilism.

disturbance in the developmental sphere of the hypophysis may be most noticeable. Again it is a well-known fact that sporadic myxedema may occur not only with its clear-cut signs and symptoms but also with its less evident manifestations known as "formes frustes." This has led authors, such as Heubner and Brissaud, to regard all forms of delayed development as dependent in large measure upon a state of dysthyroidism and to recommend therefore treatment with thyroid or thyreoidin in all these cases.

CASE II. FIGS. 150–155

A type of dysthyreogenous infantilism. Nov. 24, 1917. S. C. W., male, age 13.

Complaint.—Delayed growth and development.

The patient was referred to me by Dr. Beverly R. Tucker, of Richmond, Va., Nov. 24, 1917, with a letter in which the following facts were noted. The patient came under the care of Dr. Tucker Sept. 28, 1917. At this time the physical examination showed that the boy was 4 in. under height and 15 lb. below normal weight. His head was rather large, being 24.75 in. (64.5 cm.) in circumference. His palate was high and arched. The tonsils were somewhat infected. The head was slightly irregular, this being chiefly manifested by prominence in the region of the forehead

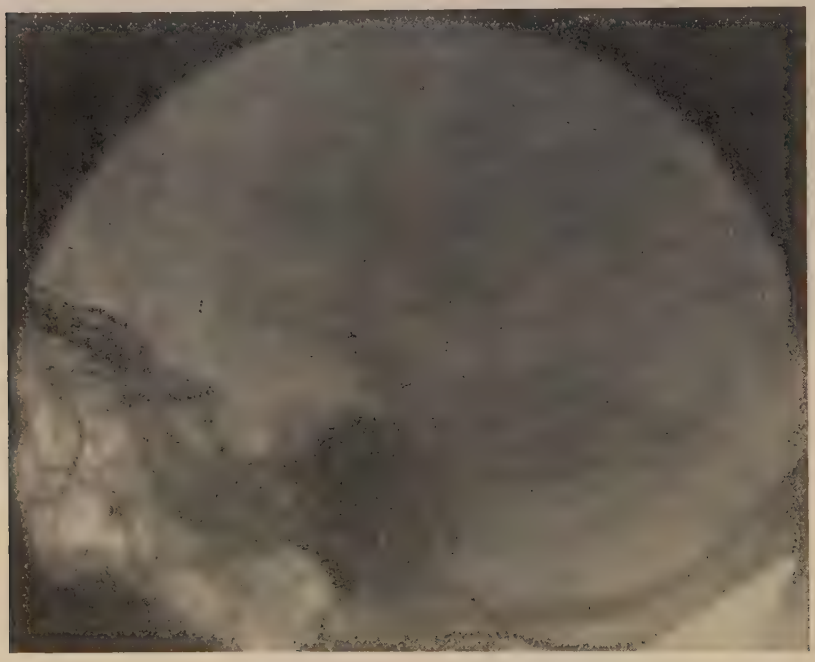

FIG. 151.—Case II. *X*-ray photograph of skull to show the sella turcica. S. C. W.; No. 37633—J. H. H. Note the huge size of the sella turcica and the marked separation of the anterior and posterior clinoid processes.

and occiput. Tremor of the hand was present. The abdomen was prominent. The genitals were under-sized.

He was mischievous and inattentive. Mental examination showed that he was backward in arithmetic, and the Binet test showed that he was one year behind the normal.

His pulse was 86. Blood pressure—systolic 94, diastolic 68. Examination of the urine, blood, and stools was negative.

The child was considered by Dr. Tucker to be suffering from polyglandular deficiency of the thyroid, pituitary, and pineal glands, in the order named. At this time the patient was taking 1 gr. of thyroid extract, and 5 gr. of pituitary extract three times daily. Dr. Tucker continued the thyroid administration, and in addition placed the patient on a therapy of pituitary, whole gland, 2 gr.; and pineal gland, ½ gr. three times a day. The patient was advised to go to school with other children. A note made one month and a half later showed that the patient had grown ⅞ in. in height; that he was doing well at school, and that his attention to his teacher was much better. His pulse was 70. The tremor of his

FIG. 152.—Case II. *X*-ray photograph of jaw to show the dentition characters in the right lower jaw. S. C. W. No. 37633—J. H. H., May 1, 1916. Age twelve years. Note the absence of the wisdom tooth, also that the germ for the permanent bicuspid is missing. The development of dentition is decidedly delayed. The latter corresponds to that seen in a child approximately ten years of age. The left lower jaw shows the same peculiarities in the dentition as shown in the plate above of the right side.

FIG. 153.—Case II.—*X*-ray photograph of left lower jaw taken Dec. 8, 1917, one year and seven months after Fig. 152. S. C. W. No. 37633—J. H. H., Dec. 8, 1917. Age thirteen and a half years. The dental characters are practically the same as those seen in Fig. 152. The development in dentition is still markedly delayed and very little progress has taken place in a year and seven months.

hand had practically disappeared. The patient was admitted to the Johns Hopkins Hospital, Dec. 8, 1917.

Complaint.—Dec. 8, 1917. Delayed growth and development.

Family History.—Father is living; has been nervous for a long time. In July, 1917, that is, about six months ago, he was operated on for exophthalmic goiter. Mother living; extremely nervous; has had a number of nervous breakdowns, due, it would seem, to hyperthyroidism. Three brothers living and well. One sister living and well. These children seem to be well developed and normal.

Fig. 154.—Case II. *X*-ray photograph of left hand taken May 1, 1916. Age twelve years. Showing undeveloped epiphyses. S. C. W. No. 37633—J. H. H., May 1, 1916. Age twelve years.

Past History.—At birth the patient was extremely blue, and when a week old suffered with jaundice. He did not develop physically or mentally, and was unable to walk or talk until about three years of age. On account of swelling of the feet he was not able to wear shoes until 2½ years of age. At two years of age, and for a period of about nine months, he was what his mother called "sickly." Three years ago he had "congestion" of the lungs. He was 15 months old when he had his first teeth and he has never gotten a complete set.

Head.—Has not suffered with headache. Has worn glasses since he was five years old. Adenoids removed at 14 months. Has had frequent tonsillitis. Tonsillectomy was not done on account of the condition of the child.

Cardio-respiratory System.—Essentially negative.

Gastro-intestinal.—No constipation; appetite good.

Genito-urinary.—Nothing abnormal.

Neuromuscular.—Patient is at times high strung and nervous. This may possibly be due to thyroid medication. Has always been under-sized and under-developed.

Habits.—Sleeps well; is playful.

Medication.—Since a child of one year has been taking thyroid extract. Later in his treatment pituitary and pineal gland extracts were added, but this therapy

FIG. 155.—Case II. *X*-ray photograph of left hand taken Dec. 8, 1917, one year and seven months after that of Fig. 154. Age thirteen and a half years. S. C. W. No. 37633—J. H. H., Dec. 8, 1917. Age thirteen and a half years. Considerable growth has occurred generally in the wrist, hand and fingers. The epiphyses however, are still undeveloped.

was not consistently carried out. The thyroid was, however, it being noted that on discontinuance of thyroid feeding the patient grew worse.

From 14 months to 8 years of age received thyroid ext	gr.	1/8	t.i.d.
At 8 years of age received thyroid ext	gr.	1	t.i.d.
From 8 to 11 years of age received thyroid ext	gr.	3	t.i.d.
At 11 years of age received thyroid ext	gr.	10	daily
From 11 to 15 years of age received thyroid ext	gr.	15	daily
For the past 2 months received thyroid ext	gr.	1	t.i.d.
Together with pituitary whole gland extract gr. 3 and pineal extract gr. 3			daily

Present Illness.—At the present time the chief complaint, as noted by his mother, is under-development, both physical and mental, and that he is not making the desired progress in either respect. She desires information and advice with regard to the patient's condition.

Physical Examination.—Dec. 10, 1917. As the patient stands stripped his form is symmetrical, but he is definitely under-sized (Fig. 150). He has a long narrow head, that is, the anteroposterior diameter is strikingly long compared with the transverse. No asymmetry of head noted. Ears small. Face is long and narrow with a depressed bridge of the nose and wide alæ. Lips are slightly protuberant but not especially thick. Features fairly good. Neck thin, short, in good proportion to the body generally. There is good proportion between the body and legs.

Abdomen somewhat full, rather protuberant, there is some flaring of the costal margin. Moderate lordosis present. Legs and arms show no excess of fat.

Measurements of Patient (Patient Stripped and Standing)

	Centimeters
Height	135.0
Circumference of head	55.3
Circumference of neck	28.5
Circumference of chest	65.5
Circumference of abdomen, level of epigastrium	62.5
Circumference of thigh, level of perineum	42.0
Circumference of calf, right	28.2
Circumference of calf, left	28.6
From jugular notch to symphysis pubis	46.0
Width of span of arms	132.3
From acromion to tip of middle finger, left	58.2
From acromion to tip of middle finger, right	58.5
(Arms at side)	
From tragus to tragus over top of head	38.0
From hair line to tip of chin	18.5
Glove measurement of hand, right	17.0
Glove measurement of hand, left	16.5
From ant. sup. spine to ext. malleolus, right	68.0
From ant. sup. spine to ext. malleolus, left	68.3

Hair.—Moderately good growth of light-yellowish hair on scalp. Eyebrows thin. Absence of axillary and pubic hair, and almost complete absence of hair on the body. Very fine lanugo hair on back. No sign of beard.

Skin.—Fairly delicate but distinctly dryer than normal; palms and feet dry. Skin on nose is dry, harsh, and rough. Skin on face smooth and warm. No edema of the eyelids, nor skin generally. Skin is elastic and nowhere shows excess of subcutaneous fat. Nails are thin and delicate. Mucous membranes are slightly pale, and there is a general pallor.

Head.—Head is symmetrical and shows no abnormal thickenings or protuberances (*cf.* *x*-ray to show enlargement of sella turcica, Fig. 151).

Eyes.—Movements and pupillary reactions normal.

Nose.—Bridge of nose depressed. No nasal discharge. No obstructions to breathing.

Ears.—Small; hearing good.

Mouth.—Tongue protruded in mid-line; slightly coated. Tongue not strikingly large. Teeth soft and second molars missing. Two upper canines unerupted. First canines are present but small; both bicuspids are missing on the upper jaw. Two first molars are missing. Teeth are somewhat irregular in shape and appear to be soft. No pyorrhea. Tonsils small; atrophic. Pharynx not injected.

Glands.—No general glandular enlargement.

Neck.—Thyroid gland, either lobe or isthmus, not palpable.

Chest.—Normal in shape and symmetrical. Examination of the lungs and heart essentially negative.

Abdomen.—Liver and spleen not palpable. Abdomen full and soft.

Genitalia.—External genitals normal in appearance. Prepuce long. Testis on left smaller than on the right and softer. Both testes descended but smaller than normal. Epididymis is palpable. Cords thin. Scrotum small. Entire absence of pubic hair.

Extremities.—Long bones and muscles fairly well developed. Fingers and hands smaller than normal, stubby and with moderately thick skin which is somewhat wrinkled. Feet small, symmetrical, well formed. There is no thickening of the long bones at the epiphyseal lines. No signs of rickets. Reflexes present, active, and equal, both sides.

Clinical Examination.—Pulse varies between 75 and 100 with an average of 85. Temperature varies between 98.2 and 99.5. *Blood count*—W. B. C. 9,000; Hb. 80 per cent.

Goetsch adrenalin hypersensitiveness test was carried out, 0.5 c.c. of the 1 : 1000 solution of adrenalin chlorid being given hypodermically. There was a mildly positive reaction to the adrenalin indicating, in the first place, that the child was receiving sufficient thyroid extract for his normal metabolism. Furthermore, the dose of 0.5 c.c., which is that calculated for adults, is a trifle large for a boy of the patient's age, particularly when he has been receiving thyroid extract 1 gr. three times a day. Should the child have been insensitive to the dose of adrenalin mentioned, increasing amounts of thyroid feeding would have been indicated.

X-ray photographs were taken of the skull to show particularly the sella turcica, which is markedly enlarged (Fig. 151); of the jaw to show the abnormal and delayed dentition (Figs. 151, 153); and of the hand and fingers to show delayed development of the epiphyses (Figs. 154, 155).

Summary.—We have, then, the case of a young boy with evident under-development both physically and mentally. There is a family history of thyroid disorder, the father having been operated upon for exophthalmic goiter. The mother is a sufferer from hyperthyroidism, which has caused numerous "nervous breakdowns."

At birth, and soon thereafter, the patient showed signs of impaired thyroid function. There was evidence of definite hypothyroidism which, in the further life of the patient, led to a condition which we have called dysthyreogenous infantilism, and which might be termed a mild cretinism.

The diagnosis rests upon the following facts. There was a failure to develop physically and mentally, and he was unable to walk or talk until about three years of age. At the same time swelling of the feet was noticed. Dentition was markedly delayed, making its first appearance at 15 months of age. In spite of thyroid medication, which was begun at 14 months of age and continued up to the present time, namely, 13 years of age, unmistakable signs of the effect of the hypothyroidism are present.

On present examination we find that the patient is 4 in. under normal height and 15 lbs. below normal weight. The skin is delicate and dryer than normal, and the nails are thin and delicate. There have been visual disturbances which have necessitated the wearing of glasses since five years of age. The head is large, long and narrow. The ears are small. The alæ nasi are flaring and the bridge of the nose is depressed. The thyroid gland is not palpable. The abdomen is full and protuberant. Hypotrichosis is present. The patient is generally under-sized.

X-ray examination shows that the pituitary gland has not escaped involvement, since the sella turcica is markedly enlarged. Dentition is delayed and imperfect as to quality. The hands and fingers are of delicate osseous structure and show delayed development of the epiphyses. The genitalia are under-sized. At times the patient is high strung and nervous, exhibiting, also, a fine tremor. These symptoms are possibly due to the thyroid medication.

The clinical examination reveals no striking abnormality. The pulse varies between 75 and 100 beats per minute, averaging 85. Blood pressure shows the

systolic to be low, 94 mm., and the diastolic 68 mm. The temperature varies between 98.2 and 99.5 degrees. Examination of the urine, blood, and stool is negative.

The adrenalin hypersensitiveness test (Goetsch) shows that upon the subcutaneous administration of 0.5 c.c. of 1 : 1000 solution of adrenalin chlorid there is a mildly positive reaction indicating that at the present time the patient is receiving sufficient medication. There is thus sufficient evidence that the patient is suffering from hypothyroidism for, were this not the case, the patient surely would have shown toxic symptoms after the prolonged, and at times rather vigorous, thyroid feeding to which he has been subjected. Again, the adrenalin test shows that this deficiency in thyroid function has been made up by thyroid feeding. In the last two months pituitary whole gland extract, gr. 3, and pineal extract, gr. 3, have been added daily to the thyroid feeding, with apparent effect of stimulating growth.

It is interesting to speculate as to what the condition of the child might have been at the present time had he not obtained the benefit which he did from the thyroid medication which was instituted at 14 months of age and has been continued ever since. It is possible that in the early years insufficient doses of the extract were given and that therefore unmistakable signs of hypothyroidism developed. It is possible that the improvement would have been greater if larger doses had been given at the beginning.

2. Hypophysis. Hypophyseal Dystrophy. (Hypopituitarism. Dystrophia or Degeneratio Adiposogenitalis (Fröhlich), Typus Fröhlich.)—In 1901 A. Fröhlich[22] drew attention to the syndrome which has since been called by his name and which is characterized by a rapidly developing adiposity, genital infantilism and myxedematous skin changes in cases of pituitary tumor. The case first described was that of a boy 14 years of age who had had headache, vomiting and rapid increase in body-weight for two years past. The adipose tissue had a characteristic distribution, the genitalia were infantile and there was an absence of hair in the genital, axillary and trunk regions. The skin showed mild signs of myxedema. Since Fröhlich's report numerous similar cases have been described particularly by Cushing[15] in his monograph on the pituitary body and its disorders.

Definition.—By hypophyseal dystrophy we understand a disease syndrome characterized by fat deposits of definite localization as is seen in eunuchs and eunuchoids by developmental retardation and often atrophy of the sex glands including both the interstitial and the generative portions with a consequent retrogressive development of the genitalia and the secondary sex characters; by the early inhibition of growth and ossification, and finally by a diminished total metabolism, polyuria and pressure symptoms oftentimes in the region of the hypophysis. The diminution or absence of function of the glandular hypophysis brought about by disease in the hypophysis itself or in its neighborhood is regarded as the primary cause of hypophyseal dystrophy. Cases of this kind have been described by Hewlett.[29]

Symptomatology.—One of the most important findings in this condition is the adiposity characterized by a very definite type of distribution similar to that found also in primary under-development of the genitalia. The similarity in fat distribution in the primary genital dystrophy and in the hypophyseal dystrophia adiposogenitalis was

first emphasized by v. Noorden.[37] The fat deposits are particularly prominent on the hips, nates, mons veneris and in the mammæ. In high degrees of such adiposity, the abdominal wall in its lower portions is particularly involved, the fat deposits being so great at times as to necessitate operative relief. Regardless of diminished nutrition and even with a certain degree of cachexia before death there is very slight retrogression in the adiposity. There are cases, to be sure, of pituitary dystrophy without adiposity but these are relatively rare. The excessive degree of adiposity is to be regarded as endogenous. This view is supported, as we shall show later, by the finding of a considerable diminution in the respiratory gas exchange in a large number of cases. The muscles are often infiltrated with fat just as is seen in primary genital adiposity and as found in animals after castration. The skin in dystrophia adiposogenitalis has a very peculiar character often described as resembling alabaster. It is strikingly delicate, sometimes dry and slightly scaly and there is a tendency to loss of hair. Occasionally myxedematous-like swellings occur in the skin. Trophic disturbances in the nails however seem to be rare.

An illustrative case described by Falta,[18] is that of a Russian girl, 16 years of age, who had a verified pituitary tumor and marked adiposity. Besides the adiposity there was found as in the typical dystrophia adiposogenitalis a retarded development of the genitals and of the secondary sex characters. In males the penis is very small and sometimes concealed in the fat folds of the mons veneris. The scrotum and testes are similarly small and the latter may be incompletely descended either on one or both sides. The prostate is also undersized. In females the external and internal genitalia are completely infantile. The labia minora are under-developed, the clitoris is short, the uterus is infantile, the ovaries are not palpable, the mammary glands are rich in fat and contain almost no gland substance, and the nipples are small and retracted. The axillary, pubic and perineal hair may be entirely absent. Menstruation and probably also ovulation occur rarely or not at all. Males remain beardless, the normal changes in voice do not occur and the vita sexualis is undeveloped. In individual instances in which the disease has occurred after the attainment of puberty the loss of beard and of pubic hair has been reported. In males impotence occurs, the menses cease in women and libido disappears in both sexes. There may be a partial retrogression in development of the genital accessory apparatus previously normal.

Metabolism.—There are relatively few researches on the metabolism in pituitary insufficiency. Instances are reported of transient polyphagia at the beginning of the disease while more often a diminution in the metabolism during the gradual development or in the excessive stages of adiposity has been noted. The basal metabolism, that is, the metabolism in hypophysectomized dogs at rest, shows a very definitely reduced respiratory gas exchange (Benedict and Homans).[6] The carbohydrate metabolism contrasts strikingly with that observed

in early acromegaly in which, in a large number of cases, the tolerance for carbohydrates is more or less reduced. This has never been found to be the case in pituitary disease producing deficient gland function but, on the contrary, the assimilation limit here seems to be definitely increased (Cushing). Falta reports several of his own cases in which the glucose tolerance was considerably above the normal. There is consequently no tendency to glycosuria. Experimentally it was shown (Goetsch, Cushing and Jacobson[20]) that when a functional pituitary deficiency is produced in dogs by the removal of the posterior and intermediate lobes of the gland, there is a marked increase in the carbohydrate tolerance as compared with that present before the deficiency was produced. In regard to the blood-sugar content results are unconvincing. The glycosuric action of adrenalin in doses of 1 mg. is absent in these cases. In other words there is an increased tolerance to adrenalin also in so far as the glycosuric response is concerned. The irritability in general of the vegetative nervous system seems to be reduced as in myxedema. Thus, for example, in many cases we find mention of dryness of the skin and of a diminished tendency to perspiration. Polyuria and polydypsia are frequently found. In fact the clinic picture of diabetes insipidus is not uncommonly seen. This is the result doubtless of interference with the secretion of the posterior lobe of the pituitary gland, a view supported by experimental evidence. This association was first pointed out by Oppenheim who showed that in gummatous diseases of the chiasm there was frequently found an associated polyuria. The body temperature is characteristically subnormal. This is probably the result of the diminished metabolism as seen similarly in myxedema, in fact all evidence speaks for the assumption that in hypophyseal dystrophy the vegetative functions are less active than in the normal man. Changes in the blood picture are common. In pituitary dystrophy there may be a slight diminution in the red-blood count or it may be normal. On the other hand, in almost all cases there is a considerable diminution in the hemoglobin content of the blood and the leukocyte count is often reduced. Changes in the differential count are however the most important. The neutrophiles are rather markedly reduced in number, the mononuclears and particularly the lymphocytes are correspondingly relatively and absolutely increased. There is a definite increase in the eosinophile cells. After operation the leukocyte count may return to normal. It may be that the mononucleosis is the expression of a mild grade of status thymicolymphaticus. Another finding, which is rather important and particularly so in the differential diagnosis, is the inhibition of growth. von Frankl-Hochwart[20] showed that in cases of pituitary tumor without acromegaly occurring in young individuals the latter were mostly of small stature. In practically all cases in which the disease begins at the transition from childhood to adolescence a retardation of growth has been noted. A great many cases of this kind have since been described.

In the pituitary and general dystrophies or in the combination of the two there are two antagonistic influences. The first, the genital disturbance, becomes apparent in the increased growth in length generally and in the greater length of the extremities as compared with the trunk. The second is a characteristic disturbance in the growth caused by disordered pituitary function. Depending upon the predominance of the first or second, corporeal measurements approach in the former those of the eunuch and in the latter instance those of an infantilism. In the severe cases the infantile character is predominate. There is a definite difference in ossification in pituitary dystrophy and in eunuchism. In the latter there is chiefly a disturbance in the closure of the epiphyses. The development of the ossification centers, however, in so far as observations indicate, seems not specially retarded, whereas there is a very marked retardation in the closure of certain epiphyses which may in fact remain open even into late adult life. The disturbance in ossification in the milder grades of pituitary disease are on the other hand not very outspoken. In the severer grades, however, the appearance of the ossification centers and the closure of the epiphyses are equally affected whereas in pure eunuchism epiphyseal closure is primarily concerned and may be delayed until well into adult life.

In addition to the manifestations of glandular disorder in pituitary disease one should mention some of the common symptoms produced by local disturbances in the region of the sella turcica produced usually by tumors, such symptoms as headaches, dizziness, disturbance in vision, optic atrophy at times, choked disc, hemianopsia, apathy, psychic disturbances, paresis of the eye muscles, symptoms depending upon hydrocephylus and paresis of the extremities The *x*-ray examination often reveals a widening of the sella turcica with destruction of the processus clinoidei and sometimes destruction of the floor of the sella. In pituitary disease there are often changes in the psyche such as a jocose temperament even in spite of severe headaches, which findings contrast remarkably with the stupidity and moroseness found in childish hypothyreosis. The patient may be apathetic and indifferent to his surroundings, when there is a complicating increased intracranial pressure. The principal anatomic and pathologic findings are those of tumor of the stalk of the pituitary gland itself or of neighborhood structures pressing upon and thus interfering with the gland. Thus internal hydrocephalus by compromising the function of the pituitary gland is frequently productive of pituitary hypoplasia and a subsequent adiposity. The individuals thus afflicted are in many cases of small stature, adipose and in many respects infantile. Neurath[36] reports instances of hydrocephalus with adiposity in children. It is possible, indeed probable, that these changes result from pituitary insufficiency brought on by pressure of the fluid in the distended third ventricle upon the pituitary gland and thus interfering with its secretory activity. Experimental extirpation of part or the whole of the pituitary gland in animals is followed by a train of symptoms which resemble in many respects or are even

precisely like the symptoms observed in clinical cases of pituitary disease. Data derived from these experiments has been very helpful in our understanding of the manifestations of symptoms in patients suffering with pituitary insufficiency (Benedict and Homans;[6] Aschner;[2] Crowe, Cushing and Homans;[14] Goetsch, Cushing, and Jacobson[24]). There is still some uncertainty as to whether the adiposity is the result of a primary pituitary deficiency or of a secondary genital disturbance. Experimental and clinic facts support rather definitely, however, the conception that there is a secondary genital under-function with pituitary under-function, and with pituitary over-function there is consequent genital over-function.

Differential Diagnosis.—In the differential diagnosis of these conditions we should attempt to determine definitely whether an existing dystrophia adiposogenitalis is of pituitary origin or is more of the nature of a simple eunuchoidism. In the latter condition there are naturally none of the symptoms of cerebral pressure and the *x*-ray examination shows a sella turcica of normal size. One must remember however, that in pituitary dystrophy sellar changes and pressure symptoms also may be absent, particularly if a gumma, tubercle, or a sclerotic process is the cause of the functional disturbance of the hypophysis. In many cases, furthermore, the determination of the respiratory metabolism may lead to a differential diagnosis. In a case of markedly diminished metabolism we would be dealing probably with pituitary dystrophy alone The ossification relationships are also of value in differential diagnosis. In a case of markedly diminished metabolism we would be dealing probably with pituitary dystrophy alone. The ossification relationships are also of value in differential diagnosis. In the primary genital dystrophy certain of the epiphyses remain open until late adult life. There are also increased growth in height and a continuation of growth beyond the normal age limits. In the more severe cases of pituitary dystrophy, on the other hand, there may be a delayed appearance of the ossification centers. Dwarfism may result but the epiphyses remain open for a shorter time. In the diagnosis of tumors of the pituitary or of its neighborhood the *x*-ray is of great help. Tumors of the pituitary body itself are apt to cause bone absorption, and even perforation of the floor of the sella turcica. Tumors of the stalk or infundibular region however are apt to cause an increased width of the entrance into the sella and of the space between the clinoid processes which as a result of pressure absorption become thinner and less evident in the *x*-ray. In tumors of the mid-brain or tumors above the pituitary stock or infundibulum the clinoid processes are apt to be thinned out and sharper than normal but less separated although in either case, with the increase in size of the tumor, confusing pictures may result. A complete erosion of the floor of the sella and of the clinoid processes may occur in either type making a diagnosis as to whether we are dealing with an intra- or extrasellar tumor impossible.

Therapy.—Operative treatment is indicated when possible for pituitary tumors. The operative results are largely aimed at the relief

of pressure symptoms arising from the increased growth of the tumor and from the internal hydrocephalus which is often present. Glandular deficiency symptoms will necessarily have to be treated by the administration of pituitary extracts. Many cases are now on record of marked improvement obtained by the feeding of pituitary tablets. Thyroid extract is sometimes given with considerable benefit for the control of the adiposity.

3. Pineal. Hypo- and Hyperpinealism.—Our knowledge of the secretory function of the pineal gland is still shrouded in mystery and until we understand more of the real function of this gland it will of necessity be impossible to determine the relationship of the latter to the development of the organism. Neither by extirpation of the gland (Dandy)[16] nor by injection of its extracts have any definite physiologic functions of this gland been discovered. There is however a somewhat general supposition that there is a close relationship between the pineal gland function and growth and sexual development. Horrax reports a stimulating effect exerted by the feeding of pineal extract on the sex glands. Cases of tumor of the pineal gland exhibiting adiposity with sexual infantilism on the one hand (Marburg)[34] and with abnormal increase in stature and precocious sexual development on the other (v. Frankl-Hochwart)[21] have been described. Whether the pineal function is primarily responsible for these interesting findings is still in doubt for with tumors of the pineal gland or its neighborhood there is usually an accompanying internal hydrocephalus which may give secondary pituitary deficiency manifestations by interference with the normal secretory process of the hypophysis which gland as we have seen is closely related to general development and the acquirement of sexual maturity. v. Frankl-Hochwart regarded the abnormal increase in stature, hypertrichosis, obesity and premature sexual development with precocious adolescence as signs of hypopinealism. If this is true, primary hyperpinealism should be associated with an infantile stature and sexual infantilism, and it is desirable that the pineal gland should be remembered when cases of this kind are met. It would seem then that the functions of the pineal gland are directly antagonistic to those of the hypophysis. It appears then that at the present time it is safe to assume that as a result of certain disturbances of pineal function clinic conditions of infantilism are produced, but that convincing proof of this is lacking.

4. Thymus.—Primary diseases of the thymus such as hypertrophies, tumors and the like are unassociated with developmental disturbances with the exception possibly of those cases in which the thymus hypertrophy and hyperplasia is an evident accompaniment of a general lymphatism as in status thymicolymphaticus. Atrophy, or other pathologic involvement of the thymus, would not be expected to lead to an outspoken developmental retardation particularly since we know from the work of Park and McClure[40] that there are no observable effects produced by the extirpation of thymus in young animals. Again primary hypertrophy and hyperplasia of the thymus itself seems

to be rare, such conditions being usually associated with a general hypertrophy and hyperplasia of the lymph tissue of the body as seen in status thymicolymphaticus and in hyperthyroidism.

It would be of advantage to consider here the question of the relationship between the thymus and the sex glands, a relationship which has not been established by experimental observation. It is probable that the persistence and hypertrophy of the thymus and the associated dysgenitalism are the result of the same primary disturbance, and that the persistence of the thymus is a secondary consequence of the primary dysgenitalism, in other words that the persistence of the thymus is merely an incidental accompaniment and not a cause of the developmental anomalies. In fact it is doubtful whether the thymus has an internal secretion and therefore it is difficult to conceive a clinical syndrome of primary hyper- or hypothymism.

Recent experiments particularly those of Park and McClure[40] have shown that the thymus is not essential to the life of the organism. Experimental controversies touched upon in the consideration of status thymicolymphaticus will not be discussed further here. Suffice it to remind us once more of the fact that in the light of recent experiments the thymus does not seem to exert an influence upon growth and development. Clinic importance of the thymus has not received very great support. Of disturbances or atrophy of the thymus in the human there is practically nothing known. A few cases of aplasia of the thymus gland in the newborn have been reported from autopsy findings. Clinically those interesting cases of thymus hyperplasia have received the most attention. In 1889 Paltauf[39] drew attention to the frequent association of thymus hyperplasia and status thymicolymphaticus with cardio-vascular aplasia and attributed the cause of death in these cases not so much to mechanical pressure as to disturbances in the vegetative sphere resulting in what he called the lymphatic chlorotic constitution. The frequent occurrence of thymus hyperplasia and hypertrophy in diseases of the ductless glands suggests that it is probably an incidental factor rather than that the hyperplastic thymus is the cause of the developmental disturbances resulting from such disease. In a few cases in which the thymus gland has been incompletely extirpated in early childhood, usually on account of mechanical pressure upon the trachea, the final results were not observed and consequently we know almost nothing concerning the effect of extirpation of the gland in the human. Similarly the importance of thymus hypertrophy in pathologic conditions is debatable. We know that thymus hyperplasia is frequently found in Morbus Basedowii as also in acromegaly, in pituitary dystrophy, in myxedema and in eunuchoidism. We thus see it present in conditions of both over- and underfunction of the ductless glands and consequently the frequent reference to the relation between the thymus and the activity of other ductless glands and between the thymus and certain abnormal developmental conditions is extremely hypothetical.

5. Pancreas.—As stated above in the discussion of true infantilism the so-called pancreatic infantilism is probably dependent upon true nutritional disturbances and not upon disturbances of the internal secretion of the pancreas. In fact disturbances in the internal secretion of the pancreas do not as a rule lead to infantilism, for in diabetes as it occurs in children, there are no accompanying evidences of infantilism in growth or in the general features. There is no retardation in ossification in cases of diabetes occurring in childhood. With the large amount of experimental work which has been done upon the pancreas such as partial and total extirpation of the gland, the ligation of the ducts with the destruction of the acinar tissue, leaving the island tissue intact, there are no instances of direct disturbance of corporeal development. Similarly there have been no clinic instances reported of retarded development upon diseases of the pancreas other than those cases which can be explained upon a basis of nutritional disturbance in which the alimentary factor is the predominant one.

6. Adrenal.—The developmental disturbances dependent upon damage to the adrenals in childhood have been too little investigated to allow of a clear differentiation from the true dystrophic types of infantilism. Hypoplasia of the chromaffin tissue appears not to lead to true infantilism. It is possible, indeed probable, that such cases of this nature belong to the so-called hypoplastic types of Bartel or to true status thymicolymphaticus. Falta[18] (p. 278) cites instances in the literature of hypoplasia of the chromaffin tissue combined with the narrowing of the vascular system, hypoplasia of the genitalia, status thymicolymphaticus and hyperplasia of the thymus gland. According to Wiesel[50] such individuals are particularly pre-disposed to Addison's disease. Acute destruction of the adrenals can occur as a result of hemorrhage, of thrombosis of the adrenal veins or of suppuration. Simple atrophy or sclerosis is however more common. The frequency of tuberculosis of the adrenals in Addison's disease should be mentioned. It is worthy of note that in infectious diseases and intoxications the adrenals are very often involved. Diphtheria toxin has a particular affinity for the adrenal. Edema, necrosis, and hemorrhage of the adrenals may occur in the infectious diseases. In many cases it seems that an insufficiency of the adrenal apparatus, and particularly of the chromaffin tissue generally leads to cardiac insufficiency. A case of v. Recklinghausen quoted by Falta is reported in which a very chronic tuberculous caseation of both adrenals was found in an 18 year old dwarf who died in convulsions. Falta would regard the tuberculous involvement of the adrenal in this case as an accidental complication, and not responsible for the dwarfism.

In cases of adenoma of the cortical portion of the adrenal in which such hyperplasia has taken place in youth abnormally rapid growth of the organism is described. There are to be found in addition premature development of the secondary sex characteristics and of the genitalia, and in adults an abnormally abundant growth of hair. As a

consequence it would appear that in those cases in which the opposite appearances are found we are probably dealing with an insufficiency of the adrenal cortex. If this grave anomaly, dwarfism, were the result of adrenal insufficiency we would have to regard it as an insufficiency of the cortex alone which would hardly be probable because we know that hypoplasia of the chromaffin tissue tends to the development of asthenic individuals of considerable stature, however. In brief then in consideration of the cases of maldevelopment which have been attributed to the deficient function of the adrenal cortex it would seem that a relationship has not been proven. It seems however, from the evidence at hand, that the adrenal cortex has a definitely stimulating influence upon the genital sphere and particularly upon the hairy development, a conception which as we shall see receives considerable support from appearances resulting from hyperplasia of the adrenal cortex. Thus, for example, tumors of the adrenal are frequently stated to be associated with adrenal over-function. The latter has been assumed because of the fact that there is in some of these tumors an increased adrenalin content. As a result of the over-function in cortical tumors of the adrenal in children we find an enormously increased development of the body and premature development of the genitalia (Falta,[18] p. 293). These over-functioning cortical tumors are probably in most cases adenomata and hypernephromata. Puberty may appear considerably earlier than normal. A careful review of the literature is found in the article of Neurath[36] (Über Fettkinder). Two representative cases as quoted by Falta may be given. The first case of Linser (Falta,[18] p. 23) is that of a boy five and one-half years old who gave the appearance of a youth and for that reason was admitted to the men's ward in the hospital. He was 138 cm. in height, the penis measured 8 to 9 cm. in length, the testes were pigeon egg in size, and the prostate was of the size found at 15 years of age. The body was adipose, the musculature was very well developed, the stature large and ossification almost complete. Dentition corresponded entirely to that of a boy 15 years of age. The length of the trunk was greater than that of the lower extremities. The childish measurements were thus preserved in accentuated form. The hypophysis was normal.

A second case of Bullock and Sequeira (Falta,[18] p. 293) is reported of a girl 11 years old who appeared like a woman of 40. At the age of 9¾ years menstruation appeared and from this time onward increasing adiposity became noticeable. The girl was 4 ft. 6 in. in height, weighed 6 stones and 3 lb., the breasts were fully developed, and the hair of the pubis and genitals was long and present in abundance. At autopsy a large tumor of the left adrenal was found consisting of cells of the zona reticulata together with numerous metastases. There were also found hyperplasia of the thyroid and parathyroid, a completely developed uterus and large ovaries with corpora lutea of recent development. The striking features of the clinic pictures in these cases, as indicated by Neurath, are the premature and excessive devel-

opment of the genitalia and of the secondary sex characters. Furthermore in all cases there is adiposity, increased growth of body often with persistence of the infantile measurement and accelerated ossification and dentition. The mental development of these children usually does not progress equally with that of the body development, and the acquirement of the sexual function is retarded.

7. Sex Glands. Eunuchoidism.—Cases of eunuchoidism are not at all rare. They are reported in the medical literature under various titles and descriptions according to whether the somatic or psychic peculiarities principally impressed the author. Thus such descriptive terms occur as dysgenitalism, infantilisme avec gigantisme, dystrophia adiposogenitalis, l'obesite d'origine genitale, Geroderma genitodistrofico, hyporchism.

Tandler and Gross[48] have adopted the term eunuchoid, which was first used by the English authors, because it is the one most generally used and because it emphasizes the similarity of this condition with the true type of eunuch. Two types of eunuchoids are distinguished, the first characterized by the eunuchoid growth in height and the eunuchoid disproportion of body which are produced by the increased growth in length of the extremities, both of the arms and the legs. We find also signs of skeletal under-development or immaturity in the open epiphyses which may remain so for years after the normal time of closure. In addition a definite saddle nose together with alterations of the pelvis and genu valgum are not infrequently found At times, the total length of such an individual is not in excess of the average, in fact it may be below this in spite of the increased growth of arms and legs. In such cases the disproportion of the body mentioned above remains as the sign diagnostic of the eunuchoid type of stature. This disproportion also distinguishes the eunuchoid type from the infantile in so far as infantilism implies the persistence of the childish corporeal proportions. The second type of eunuchoidism is characterized particularly by the eunuchoid adiposity. The skeletal disproportion, the open epiphyses, the changes in the pelvis, genu valgum and in addition the characteristic adiposity, particularly as to form and localization, are present here. Just as in the type of the castrated individual so here the deposit of fat is particularly marked on the hips, in the eyelids, in the mammary glands, in the lower abdominal regions, at the cristæ iliacæ and over the nates. The skin changes (geroderma) and the distribution of the hair correspond to those found in the eunuch. The external genitalia are small, the testes are under-developed, the seminal vesicles may be altogether absent and the prostate is small. Microscopic examination shows often retrogressive changes or even entire absence of spermatogenetic development. The epididymis may be large in comparison with the body; the testes are often composed of thick-walled tubules with small lumina. The prostate is mostly fibrous, the glandular substance being slight in amount. In fact the entire genital apparatus fails to develop. The interstitial cells may be entirely absent as shown by post-mortem examination.

The interstitial cells are replaced by an increase in the elastic fibers and in the loose connective tissue. Analogous changes are found in the female. The genital hypoplasia in most cases is associated with sterility and with the absence of normal secondary sex characters and with under-development of the mammary glands. The diagnosis in the female may be considerably more difficult, however, than in the male because of the uncertainty as to the degree of development of the ovaries and uterus. Wolff regards eunuchoidism in so far as genital hypoplasia and retardation of sex development at the infantile stage are concerned as a peculiar and for that reason interesting type of infantilism. On account of the somatic under-development in many of these cases they have been regarded as infantile in character, and the under-development of the sexual characteristics has accordingly been represented as part of the infantilism. The under-development of the sex characters is indicated by the hypoplasia of the genitals by absence of the crines pubis and by the relatively deficient deposit of fat in the lower abdominal regions and over the nates. The amount of fat accumulation is not the important thing, it is rather its localization as indicated above which is characteristic. Under-development of the mammary glands is also found. Menstrual disturbance in the older women is a common finding. An increased lymphocytosis has been described in eunuchoidism. In some cases this increase in the non-granular mononuclear blood cells may become extreme. Associated with this there has been found a decrease in the polymorphonu clear cells. Whether these blood changes are to be regarded as characteristic for states of deficient internal secretion of the sex glands one cannot say without further proof.

A definition of the clinic syndrome of eunuchoidism is not clearly observed by many authors and consequently we find many cases of infantilism grouped under eunuchoidism and *vice versa*. According to Tandler and Gross somatic infantilism is characterized by the persistence of a definite state which normally is a transient one in the developmental history and accordingly may be regarded as a morphologic anachronism which may be divided into a general or true infantilism and a partial infantilism. We are interested now in the first type characterized by the persistence of the childish corporeal form, a conception of infantilism which agrees with that of Lasègue and of Anton. This type of infantilism does not show a corporeal disproportion which is so characteristic of eunuchoids although in other respects it may show many similarities with eunuchoidism, namely, the persistence of open epiphyses, and the peculiarities of hair distribution.

The distinction from status thymicolymphaticus or the hypoplastic constitution in the sense of Bartel[4] is still very difficult; all the more so because the pathologic-anatomical symptom-complex of status thymicolymphaticus is still so little understood.

Our understanding of the changes following upon hypoplasia of the genitals has been greatly aided by the findings after experimental castration, reported by Tandler and Gross.[48] Anton[1] describes general or

dystrophic infantilism as a developmental disturbance which causes the whole organism to halt in its progress at the childish stage and which prevents the further development of an individual in the sense of his "gattung." Thus there is not only a persistence of the corporeal characters but often of the psychic peculiarities of the child as well. The somatic peculiarities of eunuchoid individuals in general correspond to those of the castrated individual and are distinguished merely in the degree of their development; thus we find not only under-function of the sex glands as shown in absence of sex characters but also changes characteristic of somatic under-development of immaturity, such as persistence of the thymus, open epiphyses, and disturbances in metabolism like those found in eunuchoid adiposity. If the under-function of the sex glands develops slowly and gradually the changes produced are much more varied in eunuchoidism than in the conditions found after castration. In eunuchoidism we are concerned chiefly with a congenital under-development of the sex glands as a result of which changes are produced which resemble those in early castration. The cases of early damage to the sex glands must be distinguished from those in which the damage to the sex glands occurs after puberty as a result of infectious diseases, such as parotitis, typhus, tuberculosis and lues. In these, changes analogous to those occurring after late castration are seen.

Tandler and Gross[48] showed that under-development or removal of the sex glands caused, besides signs of disturbances belonging to the secondary sex sphere, a general morphologic change in the organism, as, for example, the retardation of somatic maturity just as a precocious development of the gonads causes appearances which are regarded as pathologic and interpreted as an early sexual maturity. It is generally conceded now that the interstitial tissue in the sex glands furnishes an internal secretion which has a very decided effect upon the entire organism and that it is this internal secretion which is responsible for the development of the secondary characters of sex quite aside from the primary sex qualities. Certain other bodily characteristics have been found to be associated with disturbances in other ductless glands, and may resemble those depending upon sex-gland disturbance. It is highly probable that in these cases the sex glands are in many ways complimentary, a relationship we know to exist between the hypophysis and the sex glands. We know that there are two secretions of the sex glands, one derived from the gametes which is intended for the generative function and the other derived from the interstitial tissue which furnishes the internal secretion or hormone which in turn has a very definite influence upon the development of the body as a whole and upon its various organs, according as to whether this secretion is increased or diminished in amount or altered in character. There is doubtless a slight functioning of the sex glands even in embryologic life as also of the other glands of internal secretion and consequently we must credit to the former a certain degree of influence on the somatic form of the individual which effect or action must be regarded

as simply a component in the total influence of the glands of internal secretion. In other words, this view opposes that offered by some who would regard infantilism as practically primarily dependent upon a deficient sex-gland function.

8. Pluriglandular Disturbances.—The subject of pluriglandular disturbances has been considered extensively by the French. Claude and Gougerot[12, 13] were the first to emphasize the clinic conception of pluriglandular insufficiency based upon clinic observations and upon a number of pathologic-anatomic findings. Starting with the conception that under certain conditions several ductless glands become simultaneously diseased they attempted to show that in the various ductless-gland disorders symptoms are always found in the resulting clinic syndrome which indicate disorders of more than one of the ductless glands. This conception has had many followers. It has led some authors to distinguish pluriglandular syndromes with or without a predominance of symptoms referable to one particular gland. Thus many of these syndromes would show a predominance of pituitary, thyroid or genital symptoms or would be manifestly without any particular predominance of symptoms referable to any particular gland. Claude and Gougerot have furthermore extended their conception to the assumption that over-function of several ductless glands can occur at the same time or that such over-function of one gland can be combined in the clinic picture with deficiency symptoms of another. They have divided the ductless-gland disorders into seven groups depending upon the apparent predominance of the symptoms and signs referable to one particular gland, but with very definite signs pointing to involvement of several of the remaining ductless glands. As a result of these conceptions Rénon and Delille[46] have drawn very extensive therapeutic conclusions. Thus they recommend a mixed opotherapy in those cases where feeding of a single gland extract does not result in benefit. They would use, for example, the combination of ovarian and thyroid extracts or ovarian and pituitary extracts, and so on. Good results have been reported in the use of this therapy. Grasset goes so far as to say that it seems less and less likely that insufficiency of a single gland is responsible for such clinic syndromes and that the group of recognized pluriglandular insufficiency cases is becoming constantly larger and may perhaps even supplant the single gland conception. This makes the understanding of the subject extremely difficult. Falta[18] believes that the question would become much clearer if we distinguished pluriglandular insufficiency and pluriglandular syndromes on the one hand from multiple ductless-gland disease on the other for the mere presence of pluriglandular symptoms does not indicate the presence of multiple ductless-gland disease. He would like to believe, as a result of more recent knowledge, that pluriglandular symptoms may occur, first, as a result of physiologic correlations of the glands and secondly as a purely functional effect brought about through influences upon the vegetative centers. So far as concerns the physiologic correlations of the glands

there seems to be no good reason for erasing the very sharply defined syndromes resulting from individual ductless-gland disorders. Thus, as a syndrome of thyroid deficiency, we have myxedema, in which there is in addition a diminished activity of the generative glands, or again we have the typical pituitary dystrophy together with extensive degeneration of the sex glands. In each case retrogressive changes in the sex glands are component parts of the disease pictures themselves. We need have no doubts however that in the first instance the thyroid gland and in the second the pituitary assume first place in the pathogenesis of these syndromes. The disease pictures which we regard as results of pathologic correlations belong to the group of multiple ductless-gland disease. We are reminded here of the simultaneous degenerative changes occurring in the thyroid and in the glandular hypophysis and in the thyroid and the pancreatic islands. Many other examples could be given. The pathologic correlation is best exemplified in the characteristic disease syndrome similarly well defined and known as multiple ductless-gland sclerosis. We may illustrate these points by first referring to Basedow's disease. If we concede that there is a functional increase of the chromaffin tissue, we regard it as secondary in origin. Its occurrence can be sufficiently explained on the basis of physiologic correlations. It surely would not seem remarkable that, after a prolonged flooding of the body with thyroid-gland secretion, eventually disturbances in the function of the sex glands or thymus might also arise. The significance of the thymus hyperplasia is still unknown, but for that reason to deny that Basedow's disease is a clinic entity is hardly justifiable. Another example may be given, namely, acromegaly which surely is primarily dependent upon hyperplasia of the hypophysis. There are however many complicating signs and symptoms depending upon disturbances of other of the ductless glands. Nevertheless, acromegaly is rarely confused with disease of any other ductless gland. For this reason a mixed glandular therapy is undoubtedly better than the feeding of a single extract.

A clearer definition of ductless-gland diseases from purely developmental disturbances is desirable. The conception of chondrodystrophy as a ductless-gland disease is hardly warranted. Mongolianism is now regarded as the result of a degenerative process to which there is usually added a thyreogenous component. True dwarfism of recent years has been regarded as a deficiency disease of the hypophysis, a view which is hardly to be accepted generally. The most misdirected are those attempts to classify true infantilism under pluriglandular disease. Inasmuch as there has not been a real pathologico-anatomic basis for the understanding of infantilism there has been a tendency to regard it as a disturbance in the correlation of the ductless-gland system. Falta believes that true infantilism has no direct relation with the ductless-gland system. In true infantilism the organism does not develop beyond the stage of the child as a result of damaging influences during fetal or post-fetal life. In this retarded

development the ductless-gland system is involved just as the central nervous system or like every other organ of the body. There is no indication however that there is a faulty functioning of the ductless-gland system itself. This holds true also for the sex glands. They function, but only as they would in a childish organism. If they do not function at all the genitalia and the measurements of the body would be eunuchoid but not infantile.

IV. PARTIAL INFANTILISM

Several authors describe in addition to the true dystrophic type of infantilism a type which affects more directly individual organs, tissues, or systems, the so-called "partial infantilism." This type is probably identical with those forms which are considered by the older writers as due to aplasia or hypoplasia of individual organs. Since the term "partial infantilism" has come into use and has been accepted by such writers as Anton[1] and Peritz[43] it seems advisable to consider briefly those conditions which have been classified under it. Frequently the etiologic causes of the general and partial infantilism are the same, with this difference, that in the former the causative factors have acted earlier or more extensively upon the young growing organism than in the latter. Thus the causative factor in the latter, having acted later or less severely, evidences itself in changes particularly of an individual organ or system with fewer general corporeal manifestations. Thus may be mentioned hypoplasia of the thyroid gland or of the gonads. There seems to be no real reason why a new term should be given for this type. It seems that these cases could be more advantageously considered, as they have in this review, under the type of infantilism resulting from disorders in the glands of internal secretion.

On the other hand, Peritz regards as types of partial infantilism those cases characterized particularly by atrophy of the sex glands without the general manifestations of infantilism, or by cardio-vascular aplasia, or by infantile character of voice and of voice-producing organs. Cases showing absence of the beard, pubic and axillary hair and of hair in general over the body he would regard as types of partial infantilism. Again Peritz believes there is a type of pure psychic infantilism belonging to this group. This conception, however, is not generally accepted since psychic infantilism occurs so frequently in all kinds of corporeal infantilism. Peritz deserves credit however, for emphasizing the mental side of all the cases of infantilism and for pointing out the great frequency of deficiency in the realm of the psyche, as for example, in the various types of dysgenitalism. These would be types in which the psychic infantilism is combined with corporeal infantilism. Peritz, however, believes that there are types of psychic infantilism unassociated with corporeal infantilism. Here again we may be dealing naturally with partial infantilism, aplasia or atrophy of certain organs, such as the uterus and ovaries, a condition which in a young individual may have escaped notice. There are cases in which even

in adult life the whole demeanor and behavior are infantile and show the mental characteristics of a child.

The causes which may arrest the development of the psyche in infancy or childhood may be much the same as those responsible for general infantilism, but in addition there is also the factor of faulty rearing of the child, which must be considered.

V. PROGNOSIS AND TREATMENT

The final fate of the true dystrophic forms of infantilism has not been very thoroughly studied or determined. It is known, however, that on account of their pre-disposition to diseases of all kinds a large percentage die relatively early, victims of acute and chronic infectious diseases. Tuberculosis is doubtless responsible for the deaths of a large number of these unfortunate victims. On the other hand considerable good can be accomplished in those cases where the damaging influences described above can be removed or at least favorably counteracted. Undoubtedly also much can be done by placing the individual in the most favorable hygienic surroundings and under a nourishing dietetic regime. In those instances of outspoken infantilism the etiology of which is entirely obscure and probably of intrauterine origin, very little improvement can be obtained. For the psychic infantilism which so frequently accompanies the corporeal type the advantages of proper educational training and moral safeguards should wherever possible be secured.

The prognosis in those types depending upon diseases or disturbances in the realm of the glands of internal secretion is in many instances more favorable, particularly if the primary disturbance, such as tumor of a certain gland, has been removed and the symptoms of deficient glandular activity are counteracted by glandular feeding. This is particularly true of those cases of pituitary infantilism in which tumor of the gland or of its neighborhood has been surgically removed and in which subsequent feeding of pituitary extracts has been instituted. The good results obtained by the feeding of thyroid extracts in case of thyroid deficiency need only be mentioned. With the discoveries of the active principle of the ductless glands it is probable that better results can be obtained by hypodermic injections of these active principles in suitable cases. At the present time the dosage of the gland extracts or of their active principles is still upon an empirical basis and treatment must be guided by experience and by results obtained.

Glandular transplantations have offered little hope of benefiting conditions of ductless-gland deficiency, for they have been practically uniformly unsuccessful. Experimentally autotransplants have "taken" very well indeed, but in clinic conditions of glandular underactivity it is obviously impossible to obtain a graft suitable for transplantation. A mixed opotherapy, as recommended particularly by the French, has been attended by some success, in cases exhibiting pluriglandular symptoms. Combinations such as a mixture of thyroid

and pituitary extracts or pituitary and ovarian extracts have been used and improvement reported. In the cases with organic ductless-gland lesions of a surgical nature, operative measures are naturally indicated with subsequent administration of gland extract.

VI. CONCLUSION

To summarize then we may say that by the term infantilism we mean the cessation or retardation of development in which the corporeal, morphologic characteristics appertaining to infancy or childhood persist beyond the ages at which they are normally found. There are two large groups and a possible third group of cases of infantilism, namely, those belonging to the group of true dystrophic infantilism, those dependent upon primary disease of one or more of the ductless glands and those classed under partial infantilism. In the true dystrophic type of infantilism, there is more or less uniform cessation or retardation of development dependent upon a general damaging influence on all the organs and tissues of the organism, of toxic or disease origin and arising either in intra-uterine life or in early infancy or childhood. There may be a psychic infantilism combined with the corporeal type. In other cases of this dystrophic type the etiologic factors are entirely unknown.

A second large group of cases belongs to the type of infantilism caused by primary disease of one or more of the ductless glands. This type illustrates so well how important for the growth and development of the organism is the proper functioning of all the ductless glands. With the disturbance in one there are secondary disturbances in the other glands. There is however a characteristic stamp upon the disease syndrome produced by the gland primarily and principally involved and this permits of a proper diagnosis and aids greatly in instituting proper therapy. There are many instances in which the ductless glands are certainly involved, in which cases however the disease syndrome is not characteristic of a primary affection of a single gland and to which the term pluriglandular disease is applied. Finally, instances of partial infantilism are described in which individual organs, tissues or systems are more directly affected, the organism as a whole being relatively little retarded in its development.

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CHAPTER LXXXVIII

DWARFISM; NANOSOMIA; MICROSOMIA*

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A dwarf may be defined as a human being whose stature is much below the normal for his age and race. The condition of dwarfism is of some peoples a racial characteristic (racial or ethnic dwarfism) which obtains in all individuals of that race. In such a case height is controlled by inheritance. At present, races of dwarfs exist in Africa and in the New Hebrides. Tradition mentions a race of white dwarfs in Europe, contemporaneous with the Roman period, which disappeared about the tenth Century. Some have suggested that certain of the many very small individuals seen in some of the European cities, especially in the countries of Bavaria and Italy, may have descended from that otherwise extinct people. Or, dwarfism may be a characteristic of single individuals who in this particular depart much from the average of their race and who owe their small stature directly or indirectly to disease.

Our interest now lies in the individual dwarf, and in him only during his childhood, although to understand him as a child we must of necessity consider him in the light of his potential development; that is we must have the adult in mind.

Dwarfs have been classified as:

1. True dwarfs under the various titles: microsomia simplex; total dwarfism; ateleiosis. Ateleiotic dwarfs are individuals who are small in all dimensions; that is, they are fairly well-proportioned miniatures of normal persons. They have been called also "Total Dwarfs."†

2. The achondroplasic dwarf owes his short stature to micromelia; that is, to the shortness of the limbs. This, however, is not strictly true since in a marked case the trunk also is shorter than normal, although this defect is less marked than that of the legs, while the head usually is abnormally large because of a slight hydrocephalus.

3. The rachitic dwarf (p. 821) owes his short stature to a malnutrition which has led to poor general growth and especially to deformities of his limbs.

4. The myxedematous dwarfs, by far the most interesting group, are supposed to owe their condition to a lack, during the

* The best recent discussion of this subject, in connection with a very complete bibliography, is that of Rischbieth, Treasury of Human Inheritance, London, vii, (1912), Sec. xv, *A*.

† Meige and Bauer, Presse Méd., xix, No. 4 (Jan. 14, 1911).

developing period, of those internal secretions which determine growth. These individuals are retarded also in their mental and sexual development.

5. Some dwarfism is attributed to chronic diseases which begin in infancy, especially lues and tuberculosis.

6. Among the cases of so-called "infantilism" many experience such retardation of growth that they are truly dwarfs (microsoma infantilis).

Some have attempted to classify dwarfs according to the age at which the defect appears: For example: Those who are of normal size at birth, and those who are born diminutive in size. The supposition was advanced that those belonging to the former group owed their condition to some disease of infancy, usually called "rickets," and showed more marked mental and sexual retardation than the latter group and would remain sterile. This is the nanosomia infantilis, or "Peltauf's" type. They may stop growing suddenly or may grow very slowly over a much longer period than is normal. Some develop normal intelligence. Their epiphyses remain open; the secondary sex characteristics do not appear. The latter group, the dwarfs from birth, also called "primordial dwarfs," were described as well-conformed and developing (apart from size) quite normally. They are robust, usually intelligent and often virile.

This distinction between dwarfs fails since almost any of the various diseases or defects which lead to dwarfism may show its effect on growth either before birth or at a much later period. For example: In the case of infantile myxedema, dwarfism is produced by an early fetal condition (p. 808) and yet retardation in growth does not begin until after the infant is weaned.

In medicine a tendency now prevails to date a child's age from his conception, on the ground that mother and infant are, from the first, biologically, fairly separate individuals. Chemically, however, they are not separate and the mother can supply her unborn infant with some of her internal secretions through her blood, and after birth, possibly, through her milk. It is true, however, that during the nine months before birth the child may acquire almost any disease which can be transmitted through the maternal blood stream and can penetrate the placenta. Although to a certain degree he is able to defend himself against a disease of the mother, yet some diseases, such, for example, as syphilis, seem easily to invade his circulation. Such diseases may start, indeed may run a course of weeks, before birth. There is, at present, a tendency to ascribe any congenital defect to some disease of intra-uterine life. On theoretic grounds the assumption might be made that in fetal life a disease would inflict a more serious injury on the developing organism than on the growing infant, although much contrary evidence exists.

In another and more objective classification—one which assumes less knowledge of the pathology of the condition—dwarfs are grouped under the name of the author who clearly described a well-defined case

of their particular type; as the "Peltauf" type if evidently infantile; or the "Lorain" type if of more normal proportions, etc.

True Dwarfism. Ateleiosis.—In 1902 Hastings Gilford* introduced into medical literature the word ateleiosis ("not arriving at perfection"), meaning thereby incomplete development. He designated as "ateleiotic" those dwarfs formerly spoken of as true dwarfs (type "Kundrat" and "Peltauf"). This word "ateleiotic" was accepted with enthusiasm, as such terms usually are, since it would seem to express clearly in one word a medical concept formerly hazy. It is, however, one of those dangerous "semaphore" words which stretches like an arm across the track and stops our train of thought, for, using it, we are satisfied that we have expressed ourselves clearly. And yet this term implies an unjustifiedly definitive definiteness since under it are included conditions of dwarfism which as yet we are not warranted in grouping together.

The ateleiotic dwarfs have been divided into three groups: First, those in whom the condition was present at birth; second, those in whom dwarfism begins with infancy or during early childhood; and the third, those in whom it appears later, but before puberty.

Pathologic Anatomy.—Dwarfs classified as ateleiotic are to be recognized by their almost normal proportions, by the absence of deformities and of definite evidence of thyroid insufficiency, and by the persistence throughout life of the cartilage discs of the epiphyses, as can be seen in the skiagraphs. The epiphyses of many of the long bones may not develop, remaining cartilaginous as in the infant, or, if they do develop, they are, as in infancy, permanently separated from the diaphyses by cartilage, or are, at best, united to them only by thin bridges of bony tissue. The centers of ossification of the spinous and transverse processes of the vertebræ, the trochlear nucleus of the humerus, etc., centers which normally appear late, may never develop. The centers in the sternum do not unite, while the separateness of the centers of the pelvic bones persists throughout life. Histologically one does not see at the epiphyseal line the normal orderly advancing development of cartilage cells. These rather are confused while the cartilage is diffusely impregnated with lime salts.

Among the other abnormalities reported as associated with ateleiosis are osteomalacia, cysticercus cerebri, hypertrophy of thymus, etc.

Clinic Characteristics.—While ateleiotic dwarfs are symmetrical in their physical proportions and are described as "adults in miniature," yet their proportions are those of a child rather than of an adult.

Height.—The individuals are shortest in whom the defect is apparent at birth. In one such case in a child of five years, the height was 21⅞ in.; in another child of nine years, it was 19⅓ in.; in one of 12 years, 24½ in., while the height of one adult was 32½ in.

Head.—The cranium is relatively rather large, more in keeping with the physical proportions of a child than of an adult. The skull

* Gilford, Hastings, Tr. Med. Chir., lxxxv (1902), p. 305; The Practitioner, lxx (June, 1903), p. 797.

is high and brachycephalic, rather quadrant in shape and with prominent eminences. The face is short and broad. The bridge of the nose is somewhat depressed, broad and saddle-shaped, short and undeveloped. The shape of the nose is not due to premature ossification of the base of the skull, as in achondroplasia, but to defective development of the bones at the base of the skull. The lower jaw and chin are small, as in a child. Dentition is delayed, the milk teeth persisting even for years. The hair of the head is normal. No hair develops on the face of most males, and if any growth occurs the hair is thin and weak. The females sometimes have a somewhat masculine appearance. The visual organs are almost always normal. The face is infantile or child-like, without the macrocheilia, the macroglossia or the increase of connective tissue found in myxedema. The term "cretinoid" should not be used in describing the face of these dwarfs; "infantile" or "puerile" is more correct.

The neck is short, round and thick. The larynx is small; the voice is squeaky, high pitched and thin. The thyroid gland is palpable. As in the child the limbs are a little shorter in proportion to the trunk than are those of the normal adult, thus bringing the center of the body above the symphysis. Their muscles usually seem weak and yet that they can be strongly developed is proved by those trained as athletes in the theatrical companies. The limbs are of normal shape. The hands and feet are childish. No deformity of any kind is shown.

The skin is neither thick nor dry; it is indeed quite normal. A condition of sexual infantilism usually exists. The genital organs sometimes are not only infantile but even suggest a fetal condition, for example: Bilateral cryptorchism without spermatozoa in the testes, as in Schaufhausen's case, one of the first accurately reported.*

In addition to definite cryptorchism, incomplete descent of the testicles, usually bilateral, is common. The secondary sex characteristics seldom develop, such as the hair of the pubes and axillæ and, in the case of males, the beard. In the female the pelvis and mammary glands develop incompletely. These individuals usually are sterile although Gen. and Mrs. Tom Thumb (she was Lavinia Warren, a dwarf similar in type to her husband) had one child. General and Mrs. Small (Morris), "the smallest married couple in the world," had twins born to them in 1895.

Mentally these patients are shy, diffident and lack self-reliance. This may be due in large measure to the cruel humiliation which from childhood up they suffer from their neighbors. In addition to this

* Schaufhausen, Verhandl. d. Naturh. Ver. d. preuss. Rheinlande u. Westfälens (January, 1868), p. 26.

This man died when 61 years of age. He was 94 cm. tall and weighed 46.4 lb. He was of normal size at birth and showed a slight growth until 30 years of age. All the epiphyseal cartilages persisted and the sutures of the skull were open. The permanent teeth appeared at his 22nd year. He had aortic and pulmonary stenosis. His brain weighed one-nineteenth of his body-weight (in the newborn it is normally one-fifth and in the adult one-fortieth to one-forty-fourth). He was not virile. His parents were of normal size. Two of the brothers were dwarfs, two brothers and one sister were normal.

unfortunate training, however, their intelligence is, as a rule, slightly defective. That there are exceptions to this rule is suggested by such cases as Charles Stratton (Gen. Tom Thumb), evidently a man of talent and ability; by Joffrey Hudson, the celebrated English dwarf, who was considered a superior individual both morally and physically and was described as a popular and graceful courtier, one capable of commanding a Royalist Company during the Revolution and worthy to be sent by the Queen to France on an important mission; by Richard Bibson, the English miniature painter 3 ft. tall, who belonged to the Court of Charles I; and by Joseph Borwilaski who had some reputation as a scholar; by Richebord, an ateleiotic dwarf 23 in. tall who died in Paris in 1858, who, dressed as an infant and carried in the arms of a nurse, served during the French Revolution as a messenger bearing important information which he committed to memory without the assistance of records. On the other hand, Nicholas Ferry Bébé, a similar dwarf, was almost an idiot. We have not been able to verify the traditions which includes among the brilliant dwarfs Attila the Hun, Procopius the historian, Gregory of Tours, Pepin le Bref, Charles III of Naples, Godeau the Archbishop of Grasse, Doos the painter, and others. Granting that these were dwarfs there is no evidence that they were not achondroplasics and therefore not of interest to us in this connection.

Onset.—Some of the ateleiotic individuals were dwarfs at birth. This was so in the case of Hudson, who was presented, when eight years of age and but 1 ft. tall, to Queen Henriette Marie, wife of Charles I, in a pie. Nicholas Ferry Bébé was 22 cm. long at birth and weighed 14 oz. When 15 years old he was 29 in. tall.

Others are of normal size at birth but cease to grow in infancy. Among these are Charles Stratton (Gen. Tom Thumb) who, normal at birth, ceased to grow when five months old, at which time he was 21 in. tall. Nannanette Stocker ceased to grow normally at four years. She then was 33 in. tall. Years later she was described as the smallest and most accomplished woman in the Kingdom (Austria). She died at the age of 39. The woman reported by Margaret Levy* also was normal physically until four years of age, at which time her growth became slower. The secondary sex characteristics did not develop. When 44 years of age she was only 103 cm. tall, weighed 51 lb., was healthy physically and normal mentally. One brother and one cousin were dwarfs. Her skin was rough and did not sweat; there were subcutaneous pads in the supraclavicular fossæ. The administration of 100 gm. of sugar produced in 2¾ hours a glycosuria.

Course.—Sometimes those who for years apparently cease to gain in height suddenly begin to grow. Hudson, for example, when 30 years old and 18 in. tall, suddenly grew to a height of 45 in. Others, as previously mentioned, grow very slowly but continuously for years longer than the normal period, for example, until 30 years of age and older.

* Levy, Margaret, Ztschr. f. klin. Med., lxxxii (1915), p. 8.

Duration of Life.—Most dwarfs die in infancy but those who do survive puberty may live the normal duration of life or even to a very great age. Richebord died in 1858, at the age of 90; Joseph Borwilaski, of Poland, at the age of 98; while Mary Jones of Shropshire is said to have reached the age of 100. Hudson was 63 years old when he died and Therese Souvray 73.

In frequency the ateleiotic dwarfs would seem to be most numerous. Of the 73 in the cast of the Olympia Theater, London, where performances were staged in which all the actors were dwarfs, only seven were achondroplasics; all the rest were ateleiotic dwarfs.

Differential Diagnosis.—Ateleiosis differs markedly from achondroplasia since in the former the body proportions are fairly normal while the latter is a condition of deformity. True, the head of the ateleiotic dwarf is relatively a little larger and the limbs relatively a little shorter than in the adult; nevertheless both are absolutely smaller than normal and those size-proportions are normal for the child of the age at which the general retardation of development of these dwarfs has left them. These dwarfs are small, slender, weak, immature, child-like men and women. In the achondroplasia, on the contrary, the micromelia is so extreme and the hydrocephalic head so large (absolutely larger than in the normal adult) that the proportions are far from normal for any period of development and the result is, in the male, a monstrosity with large head, short crooked extremities, strong muscles, deep voice, powerful adult hairy trunk and possessed of excessive appetites and lusts. The females are fat, strong, sexually mature women. This is not quite true of all achondroplasics, for the more marked their micromelia the more puerile they are, yet even the most puerile ones are strong. In achondroplasia the important lesion is that of the epiphyseal ends of the long bones and of the bones at the base of the skull. Here there is lack of new bone formation and very premature, even prenatal, fibrosis and ossification of the epiphyseal cartilages, which obliterate them and preclude further growth. Their periosteal bone formation is that of an adult. Throughout the ateleiotic skeleton a retardation of bony growth appears and this is due to the feebleness and sluggishness of osteogenesis. This retardation in development is not limited to the bones, as in achondroplasia, but is true of the body as a whole. The bones only share in the defect which affects also the other organs.

While no difficulty in diagnosis will arise between typical cases of ateleiosis and marked cases of myxedema, yet, in certain cases, it is difficult to draw a sharp line of distinction. Indeed, the more carefully some of these ateleiotic patients are studied physically the more tempted one is to emphasize the influence of a hypothyroidism at some past if not the present period of these persons' development. This may be a superficial opinion, however. In a retarded organism the development of the thyroid would be retarded as well as, or more than, that of the other organs. But this would not affect the child's development, since the mother if she is normal in that particular, would provide the infant with this secretion. After the child is weaned, however, his own

hypothyroidism would become evident. But whether the defect of the thyroid is primary or secondary the fact is that in ateleiosis and in hypothyroidism the skeleton changes are the same; a retardation in its development and a persistence of the cartilages of conjugation so that the epiphyses remain throughout life ununited to the diaphyses. Such are the conditions in ateleiosis, in operative removal of the thyroid gland before growth is complete, in infantile myxedema and in real cretinism.

In addition to the skeletal condition ateleiotic dwarfs present several other features which seem to ally them to myxedema. The peculiar conformation of the skull, which is the same as is seen in cretins; the so-called "cretinoid" face, although most are merely puerile; the square head and face; the wide eyes; the depressed root of nose; the pouchlike lower lids, etc.; the "puerile habitus;" the defective development of the genital organs; the defect of intelligence constant in thyroid cases and common in ateleiosis; the lesions of the thyroid gland, very common in both. It is not at all impossible that infantile myxedema, cretinism and ateleiosis do merge into one another because of relations which they have in common, although what these are is not yet clear. Brissaud* classified in the one group of myxedema the "true dwarfs" and infantilism, terming the latter two conditions "myxedeme fruste."

Some cases of ateleiosis are imbecile while some cases of infantile myxedema are fairly bright. Also, thyroid medication helps other forms of dwarfism than the myxedematous. The body of the true dwarf is slender and active and many of his bodily functions are very active, while the myxedematous dwarf has a thick squat frame, thick dry skin, pot-belly, low temperature, slow pulse, thick tongue and constipated bowel. One would argue from appearances that the myxedematous dwarf might owe his condition to athyreoses while the thyroid gland of the ateleiotic dwarf only suffers along with the other organs.

Etiology.—That ateleiotic dwarfism is an inherited or at least a familial defect is evident from the fact that in the great majority of cases one obtains a history of other dwarfs in the family. There are few exceptions to this rule. Some women indeed seem predisposed to give birth to dwarfs although the defect may be inherited from the father. Borwilaski had one brother and one sister, both dwarfs; Hopkins had a dwarf sister; Therese Souvray had a dwarf sister. On the other hand, the children of dwarfs are often normal in size and especially if the mother is normal. Borwilaski's two children were normal.

Concerning the immediate cause of ateleiosis many opinions have been offered. Certainly the injurious agent, whatever it is, affects all parts of the body alike and not the bony growth only, as in achondroplasia. Rubner,† who ascribed the condition to a lack of "growth

* Brissaud, Nouv. iconog. de la Salpêtriére, x (1897), p. 240.

† Rubner, Arch. d. Hyg., lxvi (1908), p. 1.

impulse," describes the trouble as inherited inborn imperfection which modifies the functional behavior of the body cells. Some believe that there is a defect in the ovum itself which renders its development slow and incomplete so that these individuals simply do not grow up. But this certainly is not an adequate explanation since it is not at all unusual for these dwarfs to have other abnormalities than dwarfism; also their development is not at all uniformly retarded. For illustration, in the same dwarfs, mature organs and functions may be found, with others which are puerile, some which are infantile and still others which are fetal. The base of the skull may be that of a child and the vault that of an adult, while the cryptorchism sometimes present is a fetal condition. Again, the teeth not only appear late but are abnormal since irregular. The epiphyseal cartilages are not those of a child but would be definitely pathologic at any age. In the same individual some epiphyses develop abnormally, some do not appear at all, others appear but do not unite. In this particular the lesion is the reverse of that in achondroplasia in which cases the epiphyses unite too rapidly. Finally, the ridges and grooves in the bones for muscular attachments are more marked than are those of the bones of a child of the same size.

Because of the constancy of the bony lesions some have believed that the whole trouble is a bone dystrophy; others ascribe it to infection; others, to maternal intoxication, although the defect may be inherited from the father. Of course the condition is assumed by many to be the result of some defect in the organs of internal secretion, yet no evidence of this has been presented. Peltauf's case is the only one in which the sella seemed larger than normal but that of itself means very little.

Talbot* studied carefully the metabolism of a dwarf of normal proportions (although diagnosed as one with "rickets") who was seven years of age, 91.5 cm. tall and weighed 12.93 kg. (A normal boy of that age would be 114.3 cm. tall and weigh 21.9 kg.) Comparing him with boys of the same weight, Talbot found his metabolism above normal limits; but with the same age, within normal limits. He therefore decided that there was no clinical or chemical evidence of an endocrine disturbance.

* Talbot, J. A. M. A., lxxiv (May 1, 1920), p. 1225.

CHAPTER LXXXIX

CONGENITAL AND INFANTILE MYXEDEMA; ENDEMIC AND SPORADIC CRETINISM

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INTRODUCTION

The classification of the cases of cretinism as "endemic" and "sporadic," which terms are intended to convey the same meaning as when used of yellow fever, bubonic plague, malaria, etc., must, it would seem, rest on a fairly solid basis if one were to judge by its great popularity in the face of so much hostile criticism. It would indeed seem difficult to find a much better illustration of an endemic disease than is cretinism as it is found in certain very well-defined regions, the goiter districts of Switzerland, Italy and especially Austria; for not only is this condition remarkably prevalent in these localities but the observation has often been made that healthy families who move there are likely in succeeding generations to have cretin members. Surely the etiology of such cretinism must be sought in local causes. The similar but isolated cases occasionally found in other localities would naturally and properly be termed "sporadic." These terms, when used in their well-accepted epidemiologic sense, certainly do not at all imply that the pathology of the endemic and sporadic cases differs, any more than they did formerly when used of the then ever-present cases of yellow fever "endemic" in Cuba and of the few "sporadic" ones which occasionally developed in the United States. The disease was not different except in its frequency of incidence and its distribution.

But in the case of cretinism the practice has been different. Medical observers, not content to use these terms in their epidemiologic sense, have frequently suggested that endemic and sporadic cretinism are two almost different diseases. According to these writers, sporadic cretinism is the result of the congenital absence, complete atrophy, or a serious post-natal disease of the thyroid gland, while endemic cretinism is the result of a "goiterous degeneration" of this gland, due to some hypothetic local injurious conditions which obtain in the goiter regions. Some even go so far as to drop the term "sporadic cretinism" and limit the use of the term strictly to the cases which originate in these goiter regions. All similar cases which originate elsewhere they call congenital or infantile myxedema.

Barker,* for example, says: "We may definie true cretinism as an endemic disease associated with certain special regions of the earth and

* Barker, "Monographic Medicine," iv (1916), p. 895.

characterized by," . . . etc. Osler* says that two forms of cretinism are recognized: The sporadic in which the thyroid gland may be congenitally absent, is atrophied, or the condition develops with goiter; and the endemic, which occurs wherever goiter is very prevalent and which has the same clinic features as the sporadic form, that is, stunted growth and feeble mind, plus goiter.

Dock† describes the two forms separately but in much the same words and defines sporadic cretinism as "a disease nearly related to endemic cretinism and to myxedema but occurs where cretinism is not endemic," . . . etc. These and other writers, however, give almost identical descriptions of these two forms of hypothyroidism, leaving the reader in doubt as to just what the pathologic and clinical features are which justify such a sharp separation.

The most authoritative discussion of cretinism is that of Bayon.‡ He reviews the popular theory that sporadic cretinism is due to disturbances in the embryologic development of the various anlages of the thyroid gland, which either do not develop at all or only as abortive vestiges scarcely capable of function, while endemic cretinism is due to some noxious influence which produces goiter in very many of those who live in the goiter regions and cretinism in others in whom this influence has attacked the thyroid gland at the youngest possible age, in such a way and to such a degree that a hypothyroid condition is the result (thus explaining why the endemic cretin often has a definite goiter). He then states that the weak point in this theory is that such a classification does not always correspond to a difference in etiology. If, for example, the case of sporadic cretinism becomes one of the thyroid because of embryologic disturbances, surely such a disturbance would be even more likely to develop in goiter regions than elsewhere, with the result that many of the so-called endemic cases would actually, from the etiologic standpoint, be sporadic cases. If, on the other hand, the term "endemic" is to be limited to those cases in which the thyroid gland has in early life undergone degeneration, then this same condition could arise anywhere and from a great variety of causes, only, perhaps, more frequently in certain localities.

The fact remains, however, that today as well as and perhaps even more than in former years, medical authors include the geographic specification in their definition of true cretinism and, omitting the term sporadic cretinism, call all somewhat similar cases which develop outside the goiter districts "infantile" or "congenital myxedema." Added weight has recently been given to this opinion by the writings of Marine§ who considers the simple goiter (and cretinism, the extreme illustration of the same condition) as a product of the soil (poverty in iodin). If this be true, the condition would truly be endemic and these cases, since the result of a defect, would differ in many ways from those due to disease.

* Osler, "The Principles and Practice of Medicine" (1920), p. 866.
† Dock in Osler's "Modern Medicine," vi (1909), p. 448.
‡ Bayon, Verhandl. d. Phys.-med. Gesellsch. im Würzburg, xxxvi (1904), p. 1.
§ Marine, J. A. M. A., lxxvii (Oct. 1, 1921), p. 1068.

Be this as it may, however, all will agree that in the production of cretinism hypothyroidism plays some part, some stressing it as all important, some as one factor only, while still others consider it perhaps more as a result than a cause. We can, therefore, make no mistake if we describe the congenital and infantile myxedemas first, as the broader and more inclusive group.

CONGENITAL MYXEDEMA, INFANTILE MYXEDEMA, SPORADIC CRETINISM, THYRO-APLASIA

Congenital myxedema is, as the name implies, a condition due either to a disturbance of the embryologic development of the gland or to some intra-uterine disease which has either destroyed it or produced in it a "goiterous degeneration." As we shall see later a goiter when present may not be a degeneration at all nor the result of any disease but, on the contrary, evidence of a protective hypertrophy, an attempt to save the infant from myxedema. But even though the lesion may date back to the embryo when it was under 20 mm. in length; that is, even though the thyroid gland may have quite completely failed to develop (thyro-aplasia), yet at birth and even until they are weaned such children usually are quite normal in appearance, since the thyroid secretion furnished them by the mother during prenatal development, and even for months after birth, if they are breast fed, is adequate protection against that injury to bodily development which the insufficiency of their own thyroid glands would inflict. The appearance of the symptoms probably indicates the exact time when the child first begins to feel the lack of that thyroid secretion which he had been gaining through the mother's blood and later through her milk. Bayon mentions other theories for the late appearance of symptoms in the babies whose athyroidism must date back to early embryonic life; among them the vicarious action of the thymus, etc.

During the months following the weaning, the clinical picture develops rapidly. For example: Dieterle* and MacCallum and Fabyan† both have reported children with practically complete congenital thyro-aplasia. Both children appeared quite normal at birth. Dieterle's case, in which the child was not breast fed for a single day, was badly constipated for the first few weeks, was ill from the second month on, and was admitted to the Basle Clinic at the end of its fourth month, a typical case of congenital myxedema. She died 11 days later. In MacCallum and Fabyan's case, on the other hand, the child was breast fed. She developed more normally. She "nursed the breast and would eat articles of food put in her hands but could not handle a teaspoon. Said 'Papa' and 'Mamma' and seemed to recognize them, but no one else. She never walked. The mother noticed that the child's hair always was coarse and that she remained small." This child, so far as the record shows, was first seen by a

* Dieterle, Virchow's Arch. f. path. Anat., clxxxiv (1906), p. 56.

† MacCallum and Fabyan, Bull. Johns Hopkins Hosp., xvii (September, 1907), p. 341.

physician when over 10 years old, at which time he made a diagnosis of cretinoid idiocy. She died at 13 years of age.

If these symptoms appear first in the third or fourth year the condition is called infantile idiopathic myxedema, and the grade which this condition will reach will depend on how capable the injured gland is of fulfilling its function. Since in such cases the centers of ossification of the skeleton fail to appear or develop slowly, depending on the age when the defect appears, the skiagrams offer the best means of deciding whether the case is one of congenital or of infantile myxedema.

Etiology.—The cases of congenital and infantile myxedema may have an etiology similar to that of true cretinism, but theory demands that we assume that the mothers in the former cases are more normal and can protect their children chemically during gestation by furnishing them thyroid extract and that the condition which develops after birth is to be explained by the inefficiency of the thyroid gland of the infant itself.

In the family history of cases of congenital myxedema, tuberculosis, bad hygiene, a neuropathic tendency in the family and alcoholism, especially at the time of conception, are frequently mentioned. The rôle played by maternal emotions may demand more attention than it has received in the past. The mother in MacCallum and Fabyan's case blamed the condition of her child, a myxedematous idiot, to the constant terror she suffered during the last five months of this pregnancy. It may indeed be possible that such cases answer best the popular idea of "birth markings," since the abnormal balance, changed by fright, of the secretions of the endocrine organs in the mother's blood might well explain the inhibition of the normal development of the endocrine organs of the fetus. Acute athyroiditis of the unborn infant, the result of infection from the mother through the placenta, also may be suggested.

That the condition is sometimes a familial disease must be granted because of the number of families in which two such children appear. Paterson* mentioned a family in which two myxedematous children were born. This mother took athyroid extract during her third pregnancy and a healthy child was the result. MacIlwaine† reported a mother and child both of whom were myxedematous. This case, however, needs explanation since the mother's myxedema followed an attack of Graves' disease which followed directly an acute systemic infection of adult life (with diarrhea, vomiting and phlebitis) in a woman previously well. Her first child, a girl, was born four years after this previously mentioned acute illness. This child was well for one year, then, following a severe acute illness with jaundice, the symptoms of hypothyroidism began and at three years the child was a "typical cretin."

The cases of infantile myxedema, on the other hand, are supposed to result from an acute infection which leads to greater or less atrophy

* Paterson, Lancet, ii (1897), p. 849.

† MacIlwaine, Brit. Med. J., i (1902), p. 1261.

of the active gland tissue. This thyroiditis may be a complication in infectious fevers, such as measles, enteritis, septicemia, typhoid fever, etc. Bayon would lay considerable emphasis on acute infections and trauma of the thyroid gland.

Pathology.—The pathology of infantile and congenital myxedema is essentially the same as that of endemic cretinism. The skin is definitely myxedematous. The mucous membrane of the gastro-intestinal canal and of the respiratory tract are likewise affected. Many of the patients have a goiter, but atrophy of the thyroid is a rule. In some cases this organ has not developed at all, only slight vestiges of the rudimentary anlage being present. In a few cases it has been reported normal in patients who presented other lesions, such as neoplasm of the pituitary gland.

MacCallum and Fabyan's case, a myxedematous idiot 13 years of age, was so well studied that a short abstract of their findings in post-mortem examination would be of value.

The chief pathologic alterations were found in the skin, adipose tissue, thyroid, parathyroid, hypophysis, central nervous system and skeleton. The other organs showed an infantile condition but otherwise nothing of especial interest. The skin was rather thick and dull looking, hairs were scanty and the sweat glands badly developed. Repeated efforts to stain mucus in the subcutaneous tissue were without success. The adipose tissue was pale yellowish-white in color and extraordinarily abundant, forming a thick layer under the skin and loading the omentum and the other usual depots. Microscopically the fat was peculiar since it had been deposited in fine droplets in the adipose tissue cells instead of as one large drop which filled each cell.

No thyroid lobes and no isthmus were found and also no scar where the thyroid should have been. No trace on either side of either the inferior or superior thyroid arteries could be demonstrated. Two fairly large and normally appearing parathyroids lay, one on each side, at the lower limit of the larynx. On microscopic examination this parathyroid tissue was found practically normal. Just below and lateral to each of these parathyroids and at the level of the cricoid cartilage was found a small lobulated cystic structure, that on the left filled with a perfectly colorless fluid. Each consisted of several small cysts lined by flattened or cubical epithelium and containing a loose granular sort of colloid which only partly filled each and which was loaded with desquamated and pigmented cells. At one side of the cysts in each mass there was a little glandular tissue formed into acini which had scarcely any lumen. These were the very scanty remains of the thyroid lobes. A mass of definite thyroid tissue, about 2 mm. in diameter, much better preserved than those in the neck, was found at the root of the tongue just beneath its epithelium and exactly in the position of the lingual duct. This contained numerous alveoli full of colloid. The appearance of its epithelial cells indicated that this was actively functioning thyroid tissue. No other trace of thyroid tissue could be found anywhere in the body. NOTE.—The thyroid gland is developed from three anlages, unpaired median and two lateral. The median anlage appears in embryos of from 3 to 4 mm. in length as an epithelial outgrowth from the anterior wall of the primitive pharynx in close relation with the posterior part of the tongue at the position indicated by the thyroglossal duct. The lateral anlages appear on each side as epithelial outgrowths from the ventral wall of the fourth pharyngeal furrow. These three primary rudiments unite in embryos of about 20 mm. to form the thyroid body. "Comparative embryology emphasizes the significance of the median anlage as the thyroid proper."* How well this was illustrated by this girl!

* Piersol, "Human Anatomy," ii, p. 1793.

The hypophysis was larger than normal (17 by 10 by 10 mm.). Its alveoli were distinctly enlarged. This hypertrophy was due not to an increase in the amount of tissue but to the increased size of the individual cells. The alveolar arrangement was more distinct than in the normal and the colloid production more abundant.

The skeleton showed general retardation of development and of ossification of the bones, best seen in the pelvis, sternum and teeth. The bones were all slender and delicate.

The skeletal changes due to thyroid insufficiency are not at all characteristic. They consist merely of a retardation of the development of the bones, all the tissue of the bony system being equally affected. The condition is one of infantilism of the skeleton. The epiphyseal lines persist: The ossification centers do not appear at all or persist as centers. It is of historic interest that the three portions of the tribasilar bone at the base of the skull fail to unite, since in achondroplasia, a condition formerly confused with this, there is premature union of these nuclei. The epiphyseal lines persist even into old age. They appear in the roentgenograms as sharply defined lines (note the difference in rickets). Many centers of ossification are either absent or appear late. The brain has been found small with its ventricles somewhat enlarged.

Symptoms.—If the condition is congenital the child may appear normal until he is weaned. The mother in Dieterle's case, an example of quite perfect congenital athyreosis and which was never breast fed, noticed an obstinate constipation when the baby was a few weeks old. This child died in her sixth month. Once begun, the clinic picture of a myxedematous idiot practically without thyroid gland develops rapidly. If, on the other hand, the myxedema is due to an atrophy of the gland, the result of prenatal or infantile infection, or accompanies the development of a goiter, then the degree which the physical and mental changes will reach will depend on the efficiency of the injured gland.

Infantile Myxedema.—The symptoms of infantile myxedema will depend on the age when the hypothyroidism began to manifest itself and also on the degree of this insufficiency. These children may previously have shown some evidence of rickets and therefore have also that reason for deformity and the arrest of ossification.

Myxedematous (congenital and infantile) children show stunted growth and disproportion in the body development. The head is relatively large, since it is less dwarfed in growth than is the rest of the skeleton. The soft parts develop more normally than does the skeleton and so the result is a short, thick, squatty child. The skeleton, which early appeared normal in the roentgenograms, becomes cretinous. The absence of the centers of ossification of the epiphysis is first noticed in the phalanges. The fontanelles fail to close. Mental development is definitely retarded. The child fails to smile at the normal time, appears apathetic, does not begin to walk at the right age and becomes more and more like a cretin as the months go by.

The muscles are small and weak. Marked cyanosis of the skin is the rule.

The face is broad (moon-like). The profile is prognathous. The eyes are wide apart; the ears large, thick and waxy; the root of the nose is low, the nostrils are broad and flattened; the lips are thick, protruding and cyanosed; the mouth is held usually open, as a rule there is drooling, the tongue is large and often protruded; the tonsils are hypertrophied, the adenoid huge; the teeth either do not appear, or appear too late or are carious and imperfect.

The chin is short and double. The neck is short. One cannot as a rule palpate a thyroid gland but in some the gland appears normal in size while others have a goiter.

The scapulæ are winged. The spine shows a cervical kyphosis and a lumbar lordosis, therefore the abdomen is prominent, large and pendulous (a so-called "pot-belly" or "frog-belly") and is tympanitic. This is due in part to obstinate constipation. An umbilical hernia containing fat is usually present and often prolapse of the rectum occurs.

The pelvis is narrow. The genitals look infantile; the pubic hair does not grow, the labia are edematous and the uterus is infantile; there is poor development of the breasts and no pigmentation of their areolæ.

The extremities are cylindrical as a rule. The legs are short and the tibia curved, even when there is no rickets. The epiphyses are sometimes enlarged. The hands are short, thick and cyanotic; they are clumsy, spade-like or paw-like.

The skin is cyanotic, dry, cold, loose and has lost its elasticity. It is leathery, thick, yellow and wrinkled; its electrical conductivity is diminished; perspiration is often absent. It would seem edematous but does not pit on pressure.

The mucous membranes present a similar condition. The hair is coarse, dry, sparse and falls out easily. The pads, which are usually present, may be felt above the clavicles in the jugular fossæ and in the axillæ; they are soft, fluctuating masses of fat, not always symmetrically placed.

The temperature is subnormal. The patients are subject to cold. They often show a struggling respiration on account of a retrosternal thyroid which exerts compression on the trachea. The pulse is small. Nearly all of these children are anemic, their hemoglobin varying from 50 to 60 per cent. A leukopenia is the rule. They have a tendency to hemorrhages.

Chvostek's phenomenon is usually present.

These patients as a rule have a good appetite, although many have a repugnance to meat. They usually are constipated. Menstruation usually fails to appear. They walk with a swaying, unsteady gait, the head a little forward. All their muscular movements are difficult. The patella reflex is normal.

Mentally these patients are defective. The degree of the defect varies from mild imbecility to a complete idiocy, though, as a rule, it is moderate. The deafness, which is common and which may be due to

adenoids or to a middle-ear defect, is a common cause of the lack of their mental development. Their voice is rasping, their vocabulary limited. Their vision is good, the field of vision little if any contracted. These patients can be trained to some of the simpler duties of life, but most of them are dull, slow, stupid, awkward, difficult to arouse to mental or physical exertion. Sometimes they do show bursts of anger or periods of severe depression. They may be vicious or dirty or helpless.

Varieties.—These patients are best classified according to the age of onset of the myxedema and yet this is often difficult. Combè classified the cases as follows: Congenital myxedema, with complete dwarfism and idiocy; early infantile myxedema, the manifestations beginning in the first year, with some dwarfing and semi-idiocy or imbecility; late infantile myxedema, the onset during the second and third years with some dwarfism and inferior intellect; and, finally, incomplete forms of atrophic myxedema, which correspond to the myxedema of adults.

Prognosis.—The prognosis of untreated cases of congenital myxedema would seem very bad since these children seldom live more than a few years. In infantile myxedema, in which the gland function is only partially obliterated, it may be better. In both groups prognosis will depend upon the thyroid therapy and also the incidence of intercurrent infection. Not a few of these patients have reached middle life, even the age of 50.

Differential Diagnosis.—Cases of congenital and infantile myxedema when typical can be recognized at a glance or even from their portraits, but in many cases the diagnosis is difficult. One must exclude true cretinism, rickets, dwarfism of other forms, Mongolian idiocy, achondroplasia, congenital adiposity, idiocy, hydrocephalus, etc.

True cretinism (p. 816).

Rickets may be recognized by the swollen epiphyses and the irregular epiphyseal lines which can be demonstrated in the skiagrams. In typical infantile myxedema the bone formation is normal in quality but abnormally slow in quantity or comes to complete cessation. In the skiagram the clearly cut lines of the epiphyseal cartilages can be easily made out. In rickets the skin, hair, face, will be more normal there will be no myxedema, no subnormal temperature, etc. Nevertheless, the severe rachitic child is infantile and may suggest myxedema while the partial cretin without myxedema may have the definite lesions of rickets.

Total dwarfism in typical cases may be recognized by the normal proportions, for despite the diminutive size the relative proportions are those of the adult. The skiagram of the joints and bones would, however, in no wise differ from those of myxedema. Beyond this there is almost no sharp line of differentiation, for the ateleiotic dwarf usually does present one or several of the suggestive signs of myxedema. Sometimes the difference is only one of degree. A course of thyroid medication usually will decide the question. In general, however,

we would not expect changes of the skin and hair and the absence of sweating in the total dwarfs. Aub and DuBois* suggest that the difference in basal metabolism will differentiate myxedema and ateleiosis. Our experience in determining the basal metabolism of a myxedematous child has not been promising.

The question of the Mongolian idiot is a difficult one, for the etiology of Mongolism is not known and it may be, as the English insist, that he is always, or often, a case of "partial cretinism." The typical Mongolian idiot with his slanting eyes, his epicanthus, closed fontanelles, smaller tongue, more normal height and the more normal skin can be easily recognized, but the difficulty is that so many of them present only few of these signs, more being shown of those usually attributed to myxedema.

The achondroplasic dwarf should not give rise to confusion. His dwarfism is due to micromelia; that is, he has an almost normally sized muscular trunk and very short extremities with marked curves which are an exaggeration of the normal and not true deformities. His head is large, due to a true hydrocephalus; the root of the nose is deeply depressed; the hands are square, the fingers of equal length and divergent (the "trident" hand). But the achondroplasic dwarf is mentally a very alert individual. His mental age is usually that of a boy of about 12 years although some have splendidly trained adult minds. He is exceedingly active and fond of play, therefore he delights to appear on the vaudeville stage. He does not resent his conspicuous abnormalities providing he is not too viciously teased, is very jovial, is often very lustful and intemperate since he would seem to have complete maturity of the vegetative and sexual functions. The hair of the achondroplasic dwarf is normal. In fact the body usually is well covered with hair. Some of the women will raise families as large as the possibilities of cesarean section will admit. The micromelia in these cases is due to an abnormality of epiphyseal, associated with a normal periosteal, bone formation. This abnormality does not consist merely of a slowing down of osteogenesis but rather of an early fibrosis of the epiphyseal cartilages which is evidently secondary to the lack or death of cartilage cells, together with a very early ossification which unites the epiphyses to the shafts of the bones. This affects especially the long bones, the ribs and the bones at the base of the skull. The tri-basal bone may have become united even at birth, thus procluding any enlargement of the foramen magnum, while obliteration of the cartilages of the anterior portion of the occipital and the body of the sphenoidal bones prevents any increase of the length of the base of the skull. These changes in the cartilages can be recognized in the skiagrams.

The case of idiocy with infantile dwarfism can be differentiated from myxedema by the normal skin which also sweats normally, and by the absence of characteristic bone changes as well as by the changes in the configuration of his skull.

* Aub and DuBois, Arch. Int. Med., xix (1917), p. 840.

The cases of congenital adiposity may be due to a mild hyperthyroidism but the characteristic features shown in the infantile myxedema cases are quite absent.

Therapy.—The therapy of infantile myxedema is quite satisfactory provided we begin at an early enough age, best if before the child is 10 years old, provided the treatment is followed consistently and persistently. It is in these cases that we see the miracle of a little toad-like caricature of humanity developing physically and mentally along almost normal lines. In many cases, however, the mental development is not quite as satisfactory as the physical and the child does not attain his proper mental age. The physical development is sometimes so rapid that the treated child will grow 1 in. per month. At present the dried extract of the thyroid gland is used, the infant being given ½ gr. once daily; a child two years of age, 1 gr. a day, and an older child from 1½ to 2 gr. per day divided in two or three doses. If prescribed as a single dose it should be given when the child retires, and in case more than one dose is given per day the child should remain in bed after the last dose. The rise of subnormal temperature to normal is perhaps the safest criterion for the dosage since when that occurs we may assume that sufficient amounts of thyroid extract have been given. After that 1 gr. is given each day on retiring. One of the first results of this therapy is loss of weight. The skin improves because of the reduction of the myxedema and the increased activity of sweat and sebaceous glands. The hair becomes more normal, the cyanosis disappears, the pulse improves, there is less constipation and the child becomes livelier mentally and physically. This therapy is, however, not without its dangers, although the myxedematous patient is much less sensitive to thyroid medication than is the normal person. The great danger, using even small doses, is the sudden and unexpected appearance of toxic symptoms. It would indeed appear as though the drug had had a cumulative effect. The danger signals are: A sudden increase in rapidity of the pulse, feeling of weakness, of dizziness, a tendency to faint, nausea, vomiting, a sudden rise of temperature and collapse. Death in such cases is often from heart failure.

The rapidly growing bones of these children during this therapy may, it is said, become so soft that unless braces are used unfortunate deformities may result. Various calcium salts, therefore, are often prescribed in the hope of avoiding this danger.

The results of gland transplantation have never been very satisfactory. Usually there is a temporary improvement, probably during the period of absorption of the newly introduced gland itself, but this improvement soon ceases. In a case of infantile myxedema, a child 13 years of age in whose abdominal wall Dr. Willis D. Gatch transplanted a portion of the thyroid gland taken in a case of exophthalmic goiter, simultaneously operated on, the mental and nervous improvement at first seemed remarkable but it soon ceased.

These patients are very susceptible to cold and should, therefore, be protected by suitable clothes. Frequent warm baths, oil rubs, etc., are of value. They especially need sunshine and fresh air. Sea air especially is advised.

The careful control of the diet in these cases is quite important. Meat is repugnant to many and a poison to some. It should be allowed only in great moderation. The diet should consist of milk and milk products, starchy foods, green vegetables, fruit, etc. Since constipation is the rule this must be met by massage, exercise and stimulating cathartics. It will improve as a rule early in thyroid therapy.

Prophylaxis.—While the information on this point is far too meager for more than mere suggestion, yet there is little doubt that the pregnant woman with even a slight tendency to myxedema should be given careful therapy with thyroid extract, since the evidence would seem to show that her lack of the internal secretion of this gland has an analogous effect on her offspring that the lack of iodin bodies in the soil has on the inhabitants of a goiterous region.

It would also seem to be more than a coincidence that a state of continuous worry on the part of an expectant mother favors the production of a myxedematous child. These children show no disease of the thyroids but rather a marked aplasia which would suggest that some influence had prevented this tissue from its normal development. Knowing, as we do, how much strong emotions will modify the amount of the internal secretions in the blood, especially of epinephrin, it would not be surprising if this condition had a very direct influence on the development of the antagonistic glands in the fetus.

CHAPTER XC

CRETINISM; ENDEMIC CRETINISM; CRETINISMUS; CRETINOID IDIOCY

By Charles P. Emerson, M.D.

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Definition.—Cretinism ("true cretinism") may be defined as dwarfism due to retarded development associated with a greater or less degree of mental defectiveness and by fairly constant changes in the thyroid gland, bones, skin, genitals and organs of special sense and which, in association with goiter, is endemic in certain districts.

The word cretin is said to be a diminutive of the Rhaeto-Romanic word "cret" which means dwarf.

Etiology.—Cretinism is common in the regions of Europe in which severe goiter abound especially the Alpine regions of Switzerland, Austria and Italy. Less severe types may appear in any of the milder foci of endemic goiter. In Carinthia (southern Austria, with the Tyrol on the West and Italy on the South), cretins are said to number 293 and in the Salzburg region (just north of Carinthia) 276 per 100,000 of population. It is common also in Steiermark (southeastern Austria surrounding Gratz). In Italy it is common along the border of Austria and Switzerland, therefore in Lombardy, Piedmont and Venetia.

It would seem to be a disease due in part at least to a defect of environment, since members of goiter-free families which migrate to these regions are apt to develop goiter in the first and cretinism in the second and later generations. Nearly twice as many females as males are affected. Nearly all cretins have goiterous mothers or one or both parents are mild cretins, although the marriage of two cretins usually results in sterile marriage or the birth of non-viable children.

In the past it has been assumed that cretinism is very definitely, even solely, due to disturbance, that is, to subnormal function, of the thyroid gland. In later years this direct causal relationship has been doubted. Some deny any identity of cause while others say that cretinism is myxedematous cachexia combined with degeneration. One argument often quoted against the close relationship between myxedema and cretinism is the development in some cretins of myxedema following the removal of a goiter.

As to the relation between true cretinism and congenital and infantile myxedema and also that between cretinism and endemic goiter it is difficult to speak since there is so wide a divergence of opinion among those best qualified to judge. The answer will in large measure depend on one's theory of goiter. We can understand

the case of thyro-aplasia. In this the child, practically without thyroid tissue, is normal in every way until, deprived of the thyroid secretion in his mother's milk, he rapidly, unless treated, becomes a myxedematous idiot. This may explain 10 per cent. of the cretins in goiter districts. We can understand also the case of infantile myxedema for in this, the thyroid being greatly injured by disease, the child, unless well treated, suffers in much the same way as the myxedematous adult only of course more seriously, since he is a growing organism and so will suffer in his growth as well as in his functions. These two cases doubtless are common in goiterous countries, and are probably, but incorrectly, considered "typical" cretins. But goiter is present in over half the "true" cretins. This may well be proof that the child, as well as so many of his neighbors who have goiter, is, or has been, struggling against an injurious element in his environment which may, as Marine believes, be the poverty of iodin, and that the goiter is an attempt to meet this defect in the environment. The old theory which attributed the goiters of Switzerland to the use of the glacial streams as sources of drinking water was not far from correct, except that this water was dangerous not because it contained some toxin then suspected but rather because it was so pure that it did not contain the iodin salts which spring water would have leeched from the soil. The goiter of the cretin child also may be a response to the poverty of iodin in his environment, that is, in his goiterous or cretin mother's blood and milk. His defect accordingly would be much more serious than that of a case of congenital myxedema since he would feel a defect much earlier, even from his conception, than would the child of a more normal woman. In such a case the goiter instead of being an injurious factor causing degeneration of the gland would be melancholy evidence of an unsuccessful attempt at protection and adaptation. He would also be, as Brissaud* said, more a "monstrosity" than an invalid: the victim of "an accomplished fact," not of a present progressive process. He bears the marks of his mother's defect. Many of the cases of partial cretinism would suggest that the defect in the early environment of these children (their mother's blood) may have been temporary and so caused an injury to the offspring which at birth is more in the nature of a scar which he must carry through life. The milder cases would, according to this idea, not be myxedematous but inferior, that is, "second rate" offspring.

The cretins have been classified as typical and partial. One cannot, however, avoid the opinion that all typical cretins are in some degree partial since they lack wholly or in part some features of the cases of thyro-aplasia. The partial forms are: Endemic goiter, endemic deaf-mutism and endemic strumous imbecility.

Pathologic Anatomy.—One of the most striking anatomic features of the cretin is the retarded or arrested development of the bones, which interferes greatly with the normal growth of the skeleton. The extent of this retardation will depend in large measure on the age

* Brissaud, Nouv. iconog. de la Salpêtrière, x (1897), p. 240.

at which the trouble begins. No definitely pathologic process has been demonstrated in the bones; only a retardation of osteogenesis. The slow processes of ossification may continue for years and the skeleton reach maturity only at old age. That is, the condition is one of infantilism. One sees none of that abnormal proliferation of the cartilage cells in the zone of ossification which is seen in rickets, and none of the early fibrosis and ossification of the epiphyseal cartilages seen in achondroplasia. There are no periosteal changes. This retardation of development is not limited to the bones nor is that of the bones primary and responsible for the other changes in the body.

The skull may be large or small, broad or narrow. The forehead is low; the root of the nose is deep and broad owing to defective growth of the base of the skull; the malar bones are prominent and the lower jaw is prognathous. The cranial fissures remain open, the sphenoöccipital, even for 58 years. The bones of the extremities and the ribs are short, thick and often misshaped. The pelvis is narrow.

The thyroid of these patients is never normal. In 10 per cent. of the cases this gland is practically undeveloped while over 60 per cent. of cretins have a goiter. Those glands which appear of normal size microscopically show extreme atrophy of the epithelium and thickening of the colloid. The thymus often persists. There is general hypoplasia of the vegetative organs and of the muscles and an infantile condition of the sex organs.

Clinical Features.—The important clinical characteristics of cretins are their dwarfish growth, their appearance, which usually suggests myxedema, and a marked slowing up of all their mental and physical processes. At birth the cretin infant is not smaller than normal. The height of the full-grown cretin varies from 100 to 150 cm. The head is quadrangular. The face is broad, the forehead low, the eyes small and widely separated, the nose broad and flat, the nostrils conspicuous, the cheek bones prominent and the chin prognathous. The mouth looks large, the lips are thick, the tongue is large and often protrudes from the partly open mouth. The general expression of the cretin depends upon the grade of the defect; the milder cases have an Esquimo-like appearance but the face in the severer cases is positively bestial. The neck is short and thick and in 63 per cent. of the cases, as previously mentioned, a goiter is present. The body is short and broad, the thorax short and flat and the abdomen large and pendulous ("pot-bellied," "frog-bellied"). The legs are short and plump and yet the general musculature is weak. Cretins walk with a waddling, uncertain gait, on a broad base; all their movements are slow and clumsy. Some never more than creep.

The skin condition is especially important. That of many cretins has a chalky pallor although areas of brown pigmentation are sometimes present. It is cold to the touch, thick, inelastic and loose; often it is wrinkled over the forehead, hangs in folds, especially around the hips, and appears edematous, yet will not pit on pressure. In many, and especially in the older, individuals, perhaps in the majority of the

true endemic cretins, this myxedematous appearance may be absent and the skin be merely pale or yellow in color. This has been explained as the result of atrophic changes, but this cannot explain the many whose skin is not myxedematous and sweats normally. This thickening of the subcutaneous tissue is most marked in the neck, the supraclavicular fossa, where it may or may not form pads, and over the backs of the hands and feet. The skin is often dry, sweats little or not at all, and is scaly, yet in many true cretins it perspires normally. The hair, which is scanty, is thin, coarse and dry; the nails are brittle; the teeth are decayed.

The secondary sex characteristics remain more or less undeveloped. Very little axillary or pubic hair grows. The breasts of most of the women are small and menstruation as a rule is delayed or never begins. Practically all typical cases are sterile. Some, however, do reach sexual maturity when from 30 to 50 years of age and may bear children, but these usually are still-born, die early or are malformed. The body temperature is low. The vegetative functions are usually normal. Cretins are huge eaters but are careless in chewing their food and often overload their stomachs. Basal metabolism is below the limits of normal.*

Nearly all cretins show some degree of mental reduction, which varies from slight imbecility to complete idiocy and which is, in general, proportional to the lack of development of the body, as judged best by that of the skeleton and genitals. Some who appear unusually imbecile probably owe this to their deafness and to the other disturbances of the special senses so common among them and this has interfered with the mental development which they otherwise might obtain. Local observers, however, call attention to some among those who physically are typical cretins who mentally are quite up to the average of normal intelligence. That is, they are partial cretins since they have no mental defect. But the most of these individuals are dull, apathetic, stupid, indolent, lacking in memory and in decision. They are in general easy-going, although sometimes very vindictive. The higher grades called "beast men" may be trained to simpler forms of work but many become beggars or criminals, especially the mildest grades, some of whom are very irritable. The severer grades, called "plant men," have much less intelligence. The pain sense is dull but no areas of complete anesthesia are found.

Some cretins reach 50 to 60 years of age.

Partial Cretinism.—Among the same population in which endemic goiter and cretinism are common are cases showing one or more physical or mental features suggestive of cretinism but the condition is not sufficiently marked to justify a positive diagnosis. Such conditions are termed "partial cretinism." Without doubt it is this large group of partial cases, common in goiter regions but very rarely seen elsewhere, which has aided much in delineating that composite clinic picture of endemic cretinism which seems so characteristic.

* DuBois, Arch. Int. Med., xix (1917), p. 840.

Most of these individuals, but certainly not all, as Bayon has emphasized, are mentally dull, clumsy in their movements and generally lazy. Some have merely a goiter (which affects the right lobe more often than the left); others have the so-called "endemic strumous feeble-mindedness," while in still other cases there is feeble-mindedness without goiter in patients of small stature, some of whom, but not all, have very slight cutaneous signs of myxedema. Another group of partial cretins are those with the so-called endemic cretinistic deaf-mutism in individuals with no other signs of cretinism. Deaf-mutes are very numerous in all cretin regions and 50 per cent. of them have goiter. Deaf-mutism is said to be more common in Switzerland than in any other civilized country, and the same frequency obtains on the other side of the Alps, for example: In the Province of Stiermark, where there are said to be over 2000 deaf-mutes, or 1:640 of population. This deafness would seem to be due to defective development of the labyrinth, probably a result of a disturbance in the growth of the temporal bone while the skull is developing.

Prophylaxis.—The cretins present a very serious economic and social problem in goiter countries since so large a proportion of the population is physically and mentally below average and so a positive burden for the State to bear. Marine's work may offer a very valuable suggestion for the prevention of these conditions; that is, he recommends for those living in goiter regions the administration of 2 gm. of sodium iodid in 0.2 gm. doses distributed over a period of two weeks and repeated each autumn and spring. His idea is to furnish these persons that raw material for the use of the thyroid gland which in other regions the inhabitants would gain from the water.

Treatment.—The treatment is the same as that in cases of infantile myxedema. The cretin should be fed thyroid extract throughout his life (p. 814). This will certainly lead to some improvement; how much, will depend on the age and condition of the patient. It will not be nearly so satisfactory as in the true myxedema cases, since the injury even in the partial cases is in large measure a thing of the past and so will respond poorly to treatment. If the patient is young there may be an increase in height. There certainly should be an improvement in the skin, bowels, in the general nutritional condition and even possibly in his intelligence. This improvement in the case of the true cretin will not be great but any gain no matter how little is well worth the effort since it would make the patient a little less of a burden for his family and for the State.

CHAPTER XCI

RACHITIC DWARFS

By Charles P. Emerson, M.D.

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The term rickets has in the past been applied to practically all of the many conditions associated with a disturbance of bone growth. Even achondroplasia was named by Virchow "fetal rickets." The name itself implies merely a twisting, and describes the deformity rather than the diseases which may have caused it. Because the name has had so little exact pathologic significance the earlier literature with reference to cases reported as of rickets must be studied with care.

The term "rickets" as now used should be limited to a group of patients who answer in some degree at least to the following clinic picture: Head large, with cranium relatively large, quadrate or elongated and flattened on top and often with marked frontal and parietal bosses; large abdomen; an emaciated body; the musculature especially atrophic; flaccid skin; epiphyseal ends of bones enlarged; enlarged costochondral junctures; narrow chest with prominent sternum, bent legs, etc. The specific lesions of rickets are found at the epiphyseal ends of the long bones and at the costochondral junctures. Here one finds a greatly thickened, soft, bluish epiphyseal cartilage with an irregular zone of proliferation of the too actively proliferating cartilage cells, and a ragged spongy abnormally vascular line of ossification.

Since the cause of rickets is still unknown we cannot say whether or not the above clinic picture is due to only one or to several different diseases, or whether the cause of this anatomical condition may produce still others also which resemble these so little that a relationship between them is at present not suspected.

The problem of the so-called rachitic dwarfs is especially difficult. Some of these dwarfs have trunks of normal size but owe their short stature to their much twisted legs; but is the disease which has twisted these legs the rickets of Glisson and of Kassowitz? Many more symmetrically formed true dwarfs present all the signs of rickets, but is this merely a coincidence or is rickets the disease which explains their diminutive size? Since there is a general systemic disturbance which accompanies the lesions we call rickets, and which does tend to inhibit growth, we may with reason call those dwarfs with definite evidence of rickets, rachitic dwarfs, provided they do not present also evidence of some other well-recognized cause of dwarfism.

These rachitic dwarfs usually are thin, sickly appearing individuals. They are not as symmetrical, well-shaped individuals as are seen in the

cases of ateleiosis, but are always deformed. This is especially true of their lower extremities which are markedly bent, the femora with the convexity forward and outward and the tibiæ with the convexity forward (the so-called "saber shins"). The combined curves of femora and tibæ may produce bow legs or knock knees, or which is more common, some bizarre shape, since the curves of the two legs are seldom symmetrical. The arms are less distorted than the legs. The wrists and ankles are somewhat enlarged; the spine is usually bent, a kyphosis combined with a scoliosis; the chest is usually narrow above and wider below with flaring costal borders. The sternum is prominent ("keel-chest," or "pigeon breast") and the transverse groove just below the nipples (Harrison's groove) is quite exaggerated. The swollen costochondral junctures give the well-known "rickety rosary." The pelvis presents a typical deformity. Its sacrovertebral angle has been pushed down and forward and theiliac crests flare outward, thus increasing the distance between the iliac spines. This is one of the most important varieties of deformed and contracted pelvis.

Infantilism is not usually a feature of these cases; quite the reverse. It is often the venereal disease of a man or the pregnancy of a girl with deformed pelvis which brings these cases to the attention of the medical profession.

A diagnosis of rickets is still often attempted in the case of certain dwarfs who give no external evidence of this disease, since the skiagrams of their joints suggest those lesions. The possibility of recognizing rickets by means of roentgenograms alone, however, is disputed. Aub and Dubois* give a good picture of an adult rachitic dwarf who was normal until he was three years old when he became moody and his body became deformed. He began to walk and to talk at the usual age. When 38 years old his height was 123.8 cm. and his weight 37.3 kg. He certainly had no signs of infantilism. The basal metabolism of this patient was within normal limits. Meige and Bauer† present a small picture of three female adult rickety dwarfs.

* Aub and DuBois, Arch. Int. Med., xix (1917), p. 840.

† Meige and Bauer, Presse Méd., xix, No. 4 (Jan. 14, 1911).

CHAPTER XCII

PROGERIA OR MICROMEGALY

By Charles P. Emerson, M.D.

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Progeria ("prematurely old") is the term applied by Hastings Gilford* to the clinical picture presented by three persons whose condition was characterized by a curious mixture of the evidences of incomplete development and of premature old age.

Gilford called attention, first, to a group of cases of slightly accelerated senile decay which is a mere natural variation, excessive in degree, of what he called "normal senilism;" to a second group, in which this senility was a symptom of some other disease; and to a third group in which the premature senility was such a solitary and outstanding feature as practically to be a disease in itself. This is the condition he called "progeria."

In the three cases reported the disorder began without evident cause. One of the two boys reported was apparently normal until he was six months old when he began to teeth. His mother had noticed, however, that he was small and fretful before this. At that time he became emaciated; his nails shrivelled, and his hair began to fall out. When 14 years of age his intelligence was uncommonly good. During the last three months of his life he seemed to age very rapidly. The other case is interesting since the boy's mother had been almost wholly bald from alopecia areata since she was six years old. This boy died suddenly when 17 years old. The two cases reported were pronounced and were remarkably alike. The boys had the figure, face, manner and even the ideas of an old person. The height of these individuals was that of about that of a six year old child (the one was 113 cm. tall when 18 years, and the other 109.6 cm. tall when 15 years old). They were lean, weak, decrepit, and were bald with the exception that one had a sparse growth of gray or colorless hair. Their skin was dry, hard, atrophied, wrinkled and wasted, so that the underlying tendons and veins were only too evident. Some of the milk teeth persisted. They had a thin cranium, devoid of diplœ. The hair did not grow on face or pubes. They had a persistent thymus. The muscles especially were emaciated. The circumference of the head of one was 50.8 cm., of his chest in inspiration 53.4 cm. and in expiration 45.8 cm., and of his abdomen 56 cm.

During the last few years of life one of these was so easily fatigued that he had to be drawn about in a cart. While in their intelligence

* Gilford, Hastings, Practitioner, lxxiii (1904), p. 188.

they seemed to be somewhat precocious and in their sexual development a few years behind their age, yet in both these respects they may have been within the limits of normal variation.

Skiagrams of the bones showed that they had slender, thin, delicate shafts and thick epiphyseal ends which suggested childhood, although there was in some the fusion of age. These individuals presented evidence of arteriosclerosis and even symptoms of angina pectoris and fibroid kidneys.

They died, apparently from senile decay, one at the age of 17, the other at 18 and a third at 43. The post-mortem examination of one showed in the various internal organs the same extraordinary mixture of youth and of seeming old age of the organs. There was a large healthy liver, slightly contracted kidneys and shrivelled suprarenal bodies. The brain was healthy, and the stomach and intestines of paper-like tenuity. There was a persistent and degenerated thymus gland. The thyroid, pituitary and pineal bodies appeared healthy. Some lymphatic structures were normal, others wasted. There was marked atheromatous and calcareous degeneration of the coronary arteries, aorta and valves of the left side of the heart. The condition of the tissues suggested that the disease had begun after birth.

CHAPTER XCIII

MONGOLIAN IDIOCY

By Charles P. Emerson, M.D.

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Mongolism is the name applied to a well-defined group of congenital idiots who have a peculiar mongoloid physiognomy, due especially to the slant of their eyes, and the presence of epicanthus. These individuals have a round microcephalic skull, flattened occiput and fontanelles which close before the fourth month; a flat face, broad nasal bridge and prominent malar bones; oblique and narrow eye-slits and reddened eye-lids with scanty lashes; grayish-brown cheeks tinted with red; a tongue which is large, its dorsum wrinkled and its circumvallate papillæ huge. The skin is normal, not myxedematous nor dry; the hair and nails are normal. Their general musculature is soft and flabby and their joints so relaxed that their body can be twisted into remarkable attitudes. The long bones are rather short making some of these individuals below average in height although others are of fair size. Some evidence of rickets is often present. Malformations are common. The skin is normal and sweats readily. They usually are very restless and take an active interest in what is going on near them. They are, therefore, quite unlike the apathetic cretins with which some English writers identify them although some do have some cretinoid features. Indeed it may require a therapeutic test with thyroid extract to settle the question. While this group of idiots is well defined because of their appearance, yet it is by no means certain that they have a common etiology. In fact, most observers deny that this is an independent disease.

The etiology of Mongolian idiocy is unknown. All efforts to attribute the condition to disease of the thymus have failed. Many are the children of old parents (many also the last children of large families) and of parents who differ much in ages.

Pathologically a general condition of infantilism exists which may explain the persistence of the thymus. The brain has been found under-weight and deficient in its cellular make up.

CHAPTER XCIV

ADRENALS

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Anatomy.—The adrenal glands consist of two paired bodies lying at the anterior poles of the kidneys. Each comprises two distinct parts which differ in their staining reactions, their origins and their functions. Although these two components, the cortex and the medulla, are intimately united, it is doubtful if the association is more than an anatomical accident. In different animals all gradations from morphologic independence to the most intimate association are found. In fishes the homologues of the adrenal glands comprise two distinct entities, the inter-renal and the chromaphil bodies, corresponding, respectively, to the cortex and the medulla of the higher forms.

Histology.—The *cortex* is made up of three concentric zones. The outer is the *zona glomerulosa* or *externa;* the middle, the *zona fasiculata* or *media;* and the inner, the *zona reticularis* or *interna.* Throughout the three zones the cells are arranged in more or less definitely radiating columns. Toward the outer surface of the gland these columns end in rounded terminations somewhat resembling the glomerulæ of the kidneys. In the zona interna the columns break up into a reticulum formation. In the human fetus this zone is relatively very thick and gives to the gland as a whole a great weight as compared with that of the adult.

When treated with osmic acid the adrenal cortex assumes a dense black color, a fact which indicates that fat or fat-like material predominates in the cells. Further tests show that this consists of fat, proper, which appears as globules of various sizes together with doubly refracting crystals of lipoid substances, supposedly lecithin and cholesterol. The latter is in the form of esters. The amount and distribution of these lipoid bodies varies greatly in different animals. They have been regarded by many as secretory products. Elliott and Tuckett found that the cholesterol bodies increase during rest and diminish during muscular activity. They report, also, that the doubly refracting lipoids are absent from the fetal cortical cells. In various diseases the lipoids are likewise depleted. On the other hand, a doubly refractive material is conspicuous in the hypertrophic cortical cells characteristic of pregnancy.

Fixatives other than osmic acid give rise to a wide variety of granular appearances in the cortical cells. Numerous attempts to correlate

the cytologic picture with states of secretory activity have been made but, so far, without results that are generally accepted.

The *medulla* of the adrenal is composed of cells that differ strikingly from those of the cortex. In material fixed with chromium salts a characteristic brown or yellow color is seen. Hence the medullary tissue, together with that of a similar nature outside the adrenal proper, is often designated the chromaffin tissue. The medullary cells are polyhedral in shape with central nuclei. They are arranged in masses among which sinusoid blood spaces permeate. The bases of the cells come into very close relations with the sinusoids. The medulla contains a number of different sorts of granules which vary in size and number in different cells. The most prominent of these are the chromaffin granules which give rise to the characteristic secretion, adrenin. Lipoid and pigment granules also are found whose functional significance is quite unknown.

Blood Supply.—The adrenal is relatively the most vascular organ in the body, receiving about six times its weight of blood per minute. The arteries, several in number, enter the cortex at various places and penetrate the gland in the connective tissue septa between the cell columns, giving off capillaries. Reaching the *zona interna* the arteries terminate in sinusoids which communicate with those of the medulla. The venous outflow is largely into a lumbar vein which crosses directly over the gland. Cow has recently reported that certain venules lead directly to the kidney, permitting the secretion to reach it and affect its function before entering the blood stream.

Nerve Supply.—Numerous nerve filaments enter the gland partly from the splanchnics directly and partly from the neighboring plexuses. The fibers are largely or exclusively true sympathetics. They are distributed both to the cortex and to the medulla, but predominately to the latter. Some go to the blood-vessels, and others are distributed to the cells directly. This distribution would indicate that the gland receives both vasomotor and secretory fibers, a matter upon which physiologists are not decided. The nerve supply to the adrenal is unique in that the preganglionic neurones reach the gland directly instead of connecting in a sympathetic ganglion with a post-ganglionic cell. This would indicate that the medulla takes the place of the ganglion, with which it is, in fact, embryologically homologous.

Accessory Adrenal Tissue.—The adrenal proper comprises by no means all of the chromaffin or the inter-renal tissues of the body. "Accessory adrenals" occur in widely separated places. This condition is apparently brought about largely by the migration of the sex glands in close association with which the cortical tissue arises. Closely associated with the ganglionated sympathetic nerve cord occur masses of tissue which give the characteristic brown chromium stain of the adrenal medulla. These are known variously as *paraganglia, chromaphil bodies* or *chromaffin bodies*. They vary greatly in size. In a newborn child they reach a length of 1 to 1.5 mm. The individual ganglion may have one or several of these bodies associated with it.

Other chromaffin masses are found associated with the different abdominal plexuses. The largest of the chromaffin bodies lies retroperitoneally along the aorta. This is a paired structure, each lobe of which, in the newborn infant, is about a centimeter in length. The *carotid body*, which has been known anatomically from the time of Haller, probably also belongs in this category, although it is rather more definitely organized than most of the accessory bodies. It has a rich nerve and blood supply. Little is known as to the functional significance of these accessory chromaffin bodies. They are strikingly more prominent in fetal than in later life. From the abdominal chromaffin body has been obtained an extract that gives a vasomotor reaction apparently identical with that of adrenin.

Embryology.—As previously mentioned, the cortex and medulla arise independently and later become associated to form an adult gland. The process begins at an early stage when the embryo is about 6 mm. in length and continues until late childhood. A mass of primitive cortical cells is first set apart and this is subsequently invaded by the medullary elements.

The cortical cells appear as a series of buds which arise from the celomic epithelium in the dorsal body wall. These buds grow inwardly into the mesoderm and lie ventral to the aorta. The process begins at the 6 mm. stage; at 8 mm., the glands are definitely separated from the parent tissue and at 9 mm. have acquired their own blood supply. Later, the buds fuse and form a ridge of tissue projecting from the wall at the root of the mesentery on each side, just medial to the mesonephros. The suprarenal ridge thus formed extends as far forward as the dorsal pillars of the diaphragm and reaches almost the full length of the body cavity. Later, by a process of degeneration of some of the tissue and arrest of development while the remainder of the body continues, the glands come to have the relatively small size of their adult state. The differentiation of the cortex into the three layers of the adult does not occur until the later years of childhood.

The chromaffin system is differentiated from the primitive nerve tissue. At an early stage of development a mass is separated off from the lateral wall of the neural plate to form the neural crest. From this mass cells migrate to the neighborhood of the aorta. By the time the embryo has reached a length of 7 mm. the migration is well under way. At 9 mm. the ganglionated cord and the sympathetic nerve plexuses can be recognized. At 16 mm. the outlying visceral ganglia have been established. In close association with these structures are the cells which give rise to the chromaffin system. Indeed, in the earlier stages, the two sorts of cells are indistinguishable. They form together the sympatho-chromaffin tissue. Later as the two types become recognizable they form the sympathoblasts and the chromaffinoblasts. The chromaffin bodies develop early before the sympathetic cells proper or the medulla of the adrenals are differentiated. When the embryo has reached a length of 19 mm. the chromaffin cells have begun to penetrate well into the cortex mass. At 9.5 cm. the chromaffin cells appear as

islands scattered through the cortical tissue, but some of the cells have already reached the central vein and formed the nucleus of the medulla. From this stage on, development consists of further penetration of the chromaffin cells to join the central mass. The process is not entirely completed at the time of birth.

Physiology.—The first significant contribution to our knowledge of the functions of the adrenals was made by Addison when he discovered the relation of the glands to the disease that bears his name. Addison's disease is characterized by an insidious onset, with muscular weakness, pigmentation of the integument, digestive disorders, hypothermia, nervous disturbances and arterial hypotension. The hypotension is probably due merely to the cardio-vascular apparatus being involved in the general muscular weakness. Addison's discovery led to numerous attempts to duplicate the clinical symptomatology in the laboratory. This experimental work, however, led merely to a somewhat profitless controversy as to whether or not the adrenals are essential to life. The experimental difficulties were chiefly two. Certain animals, notably the rat, which was largely used, are well supplied with accessory adrenal tissue and are able to dispense with the glands proper with little or no resultant symptomatology. Cats and dogs, on the other hand, die within a few hours to four days in a state of profound muscular and circulatory depression. In this latter case the time is not sufficient for the development of the classic Addison manifestations. Attempts to cause a more slowly developing adrenal deficiency by fractional extirpation of adrenal tissue or the injection of escharotics have not led to any very satisfactory results.

In 1894 Oliver and Schafer, and two years later, Szymonowicz, independently discovered that the injection of adrenal extracts by vein leads to a striking reaction. The blood pressure rises, often to twice the original level, and the heart beat becomes slow and powerful. If the vagus nerves are cut, however, the beat becomes both rapid and powerful, leading to still greater augmentation of pressure. The hypertension is due both to augmented heart action and to vasoconstriction of peripheral arterioles. From such observations the conclusion was drawn, and is still widely held, that adrenin, the so-called "active principle" of the glands, is a general vasoconstricting agent.

In 1915, however, Hartman made the significant observation that a given dose of adrenin produces materially different effects depending upon whether it passes through the splanchnic or the somatic vascular areas. When the splanchnic vessels are tied off, injection of an amount of adrenin which normally produces a rise in pressure causes either a much slighter effect or an actual fall. Hoskins and Gunning found further that, in the somatic circulation, a given dose of adrenin produces simultaneous vasoconstriction in the skin and vasodilation in the underlying muscles, the total effect depending upon whether constriction or dilation predominates. As a general rule, with smaller doses the latter is true, and a fall of general arterial pressure results, whereas, with larger doses, the vasoconstriction and the resulting,

better known hypertension is observed. In skeletal muscle very large doses convert the dilation to contraction. In some of the viscera only contraction has been observed. It is therefore no longer permissible to refer to adrenin as a vasoconstricting agent. It is either vasoconstricting or vasodilating, depending upon the amount used and the organ concerned, as well as several attendant circumstances.

From adrenal extracts Abel in 1897 isolated in pure form a benzoyl addition product of the characteristic chromaffin secretion. This he named *epinephrin*—a term that has since come to be widely used in the United States to refer to the actual secretion itself. In 1901 Takamine and Aldrich each isolated the secretion as such. To this the name *adrenalin* was applied. In the greater part of the world this is the term most frequently used. Perhaps as a generic term *adrenin* would be most satisfactory.

Chemically, adrenin has the formula $C_9H_{13}NO_3$ or, $C_6H_3(OH_2) - CHOH - CH_2 - NHCH_3$. It is, therefore, dioxyphenyl-ethylol-methylamin. Its formula suggests that it may be derived from tyrosin. It is now produced synthetically.

Adrenin is a substance of remarkable potency. By certain biologic tests it is possible to demonstrate its presence in dilutions of one part in a billion, and its detection in a strength of one part in ten millions is relatively easy. Large doses are correspondingly toxic. One milligram per kilogram body-weight given by vein commonly results in death from pulmonary edema, paralysis of the heart or respiration. A slower intoxication is accompanied by hemorrhages from the intestinal mucosa.

Following Oliver and Schafer's and Abel's studies the next contribution of major importance was made by Elliott in 1905. He tested systematically the effects of adrenin in the various organs throughout the body. He showed that it stimulates selectively the neurocellular endings of the sympathetic nerve fibers, or, more specifically, the neurocellular junction substance, wherever found. The effect, at least in physiologic quantities, depends, in any organ, upon three factors: If the structure receives no sympathetic fibers, no reaction occurs. If it has a sympathetic innervation, but this in every day life is little used, the effect of adrenin is correspondingly slight. Finally, the effect is either augmentation or depression of function, depending upon whether the sympathetic fibers to the organ are stimulatory or inhibitory. Thus the heart is stimulated while the gastro-intestinal tract, with the exception of the sphincters, is depressed.

Other structures which react to adrenin by increased function are the uterus, especially in the pregnant state, the sphincters of the alimentary canal, the kidney, the liver (glycogen discharge), the bladder (variably), and the dilator pupillæ. The broncho-constrictors and the arterioles of the skeletal muscle share in the depression of activity seen in the alimentary tract.

The problem of the control of adrenal secretion has received a great deal of attention. It was shown by Dreyer that stimulation of the

splanchnic nerves causes an augmentation of the pressor quality of blood taken from the adrenal veins, a phenomenon which he rightly interpreted as indicating augmentation of adrenin discharge. Whether this is due to the action of secretory nerves proper, however, or merely to resultant vasodilation in the glands, is still undetermined.

The adrenals receive their innervation through the splanchnic (sympathetic) nerves and hence, supposedly, are influenced by the various conditions which cause augmented sympathetic functioning. Strong emotion of any sort commonly results in a marked outflowing of sympathetic impulses. This fact led Cannon in 1910 to a hypothesis that one potent cause of adrenal activity is emotional excitement. Put to the test, the hypothesis has been supported by numerous observations, especially by Cannon and his students. Stewart and Rogoff, on the other hand, have been unable to confirm some of these. Perhaps the most significant single test of the hypothesis is by means of the denervated heart of a dog or cat. When the cardiac nerve paths, both vagus and sympathetic, are interrupted, the heart becomes very sensitive to adrenin. Emotional excitement, in such an animal, causes a striking acceleration of the pulse, an effect which cannot be due to nerve impulses under the conditions. Similar results follow from painful sensory stimulation or from asphyxia. Without going further into the controversial literature of the subject it may be stated that the preponderant mass of available evidence indicates that strong emotions, pain and asphyxia cause a discharge of adrenin which reinforces the sympathetic activity characteristic of such periods.

This results in a number of reactions that are of obvious utility in coping with stressful conditions and in integrating the body for combat or flight. Quiescence of the digestive system and shifting of the blood from the splanchnic to the somatic structures, especially the muscles, follows; and the speed of circulation increases. Dextrose is mobilized in augmented quantity. The bronchioles are dilated, permitting freer breathing. Most striking, perhaps, is the fact that muscular fatigue is remarkably lessened. Gruber has shown that the activity of a fatigued muscle may immediately be doubled as a result of the administration of a small quantity of adrenin. This may occur without any improvement of the local circulation. The recovery from fatigue is also markedly hastened by adrenin.

A decade ago it was taken for granted that, since adrenin is a powerful pressor agent and since adrenal extirpation results in a striking vaso-depression, the essential function of the glands is to keep the blood supplied with an adequate amount of adrenin and thus keep up blood pressure. By analogy it was assumed that the sympathetic system in general is kept thereby in a state of partial stimulation. This is the so-called "tonus theory."

But the theory is now untenable. If blood pressure were dependent upon the stimulatory effect of circulating adrenin, a slight addition of the amount should cause increased pressure. Instead, small doses of adrenin are depressor. Circulating adrenin is quickly destroyed,

hence the tonus theory presupposes its constant formation. Ligating the adrenals should, therefore, cause an immediate fall of pressure. This does not occur. Injections of adrenin in quantity sufficient to affect blood pressure at all paralyze the stomach and intestine. Obviously, blood pressure could not be long maintained at the expense of complete ileus. Other a priori evidence in considerable amount might be cited. As a matter of fact, direct evidence supports the same conclusion, that circulating adrenin plays no essential rôle in ordinary body functioning.

Stewart has repeatedly observed that if one adrenal of an animal is removed and the other denervated, it is no longer possible to bring about any detectable discharge of adrenin. The animal continues alive and in excellent health, but if the remaining adrenal is removed, death inevitably follows. The life of the animal cannot be significantly prolonged by adrenin administered in any known way. Hence, its death under such conditions cannot be ascribed to depletion of this substance in the circulation. Moreover, the extra-adrenal chromaffin tissue still remains. The conclusions follow that adrenin plays no essential part in ordinary functioning and that it is merely a reserve resource for augmenting sympathetic activity in times of special need.

The cause of death following adrenal extirpation, then, must be sought in some other direction. Years ago it was believed that death is due to a toxemia resulting from failure of the glands as a detoxicating mechanism, but, if so, the toxin should be easily detectable, especially since it is potent enough to kill a dog within a few hours. In the older literature are several reports that such a toxin can be demonstrated. Later observers, however, in experiments in which toxic post-mortem decomposition products were excluded, have found the blood of animals dying of adrenal deficiency quite innocuous. We are thus thrown back to the vague conception of a failure of tissue metabolism as the most probable cause of death. The tissues that first exhibit weakness are the skeletal and cardiac muscles. Hence, their failure is probably the fundamental feature. Thus, it would seem that the adrenals contribute to the blood stream some unknown substance necessary to the metabolic processes of the contractile tissues.

The best evidence indicates that this substance is derived not from the medulla but from the cortex of the gland. Biedl has performed extirpation experiments upon eels, removing the inter-renal tissue which corresponds to the adrenal cortex in the mammal. This operation resulted in progressive muscular weakness ending in death. The attempt has been made also to perform differential extirpations in mammals, leaving either cortex or medullary tissue intact. Decreasing the amount of medulla caused little or no effect, but when the cortical tissue was reduced below a certain critical amount death ensued. Boyd has recently described a case in which a comparable condition came about clinically. An autopsy was performed on a soldier who had died of "acute adrenal insufficiency." The adrenal tissue on one side was completely destroyed. On the other side only a

strip of cortex remained. The microscopic picture indicated that the medullary tissue had been destroyed for a considerable period, and yet the patient had been able to engage in full military activity. However, when the cortical tissue had been reduced below the critical amount, death ensued.

Little is known as to the nature of the material contributed by the cortex. Earlier mention was made of its striking content of lipoid substances. Voegtlin and Macht have succeeded in isolating from the cortex a substance, different from adrenin, which is a potent vascular stimulant, but the actual significance of the substance as a factor in physiologic or pathologic functioning has not been determined.

From a clinical point of view, interest in the adrenals centers largely in Addison's disease. Little has been added to our essential knowledge of its etiology or symptomatology since Addison's own masterly description in 1855.

The disease is rare and affects men more frequently than women. It is most common in the third and fourth decades of life, very rarely occurring before 15 or after 60. As etiologic factors alcoholism, intoxications, trauma and heredity have been noted, but by all odds the most important is tubercular infection. Syphilis also seems to play the etiologic rôle occasionally.

The pathogenesis is obscure. Cases have often been described in which, at autopsy, little or no adrenin could be detected in the glands. Since adrenin spontaneously disappears soon after death, this finding may be of little significance. More convincing is the fact that the medullary tissue itself is often necrotic or even completely absent, while the cortical tissue is little affected. Were it not for the presence of relatively large amounts of extra-adrenal chromaffin tissue, such findings would seem significant. In other cases, however, the cortex has been found defective, while the medulla appeared more or less normal. In a small percentage of the cases both medulla and cortex have been found approximately normal in appearance, the associated sympathetic nervous apparatus being primarily affected. Wiesel has argued that cases in which the medulla is defective are characterized by adynamia whereas cortex deficiency is associated with digestive disturbances and nervous symptoms.

As early as 1895 Starr called attention to the fact that Addison's disease may be accompanied by a condition of status thymolymphaticus. The association is so frequent as to suggest causal relationship, but specifically what this may be is completely unknown. Conversely, in cases of thymus hypertrophy, small adrenals are commonly found.

The symptoms of Addison's disease are primarily asthenia, digestive disturbances and melanoderma. All of these are subject to striking fluctuations in severity. The asthenia may be very profound, the patient lying almost in a stupor, caring neither to speak nor eat. Psychic adynamia with impaired memory may be included, though states of excitation may also be seen, leading to irritability and quarrelsomeness. Insomnia alternating with marked drowsiness

is noted occasionally. Fainting is not uncommon. This is supposedly due merely to the very low blood pressure characteristic of the condition.

The digestive disorders, although usually prominent, may be completely absent. Among these are meteorism, abdominal pain and tenderness, anorexia, or at times abnormal hunger, nausea, vomiting, hyperacidity and constipation or diarrhea.

The pigmentation appears gradually, and is often the first symptom. It varies from dirty-yellow through browns to an actual black. It may be diffuse but is most pronounced in areas normally pigmented. Parts of the body surface exposed to friction or pressure are especially affected; a zone around the waist under the belt is very common. Diagnostically, much importance attaches to the presence of pigmentation in the folds of the palms and fingers and in the mucosa of the mouth, lips and palate. Pigmentation, however, is by no means pathognomonic; it may be absent in undoubtedly positive cases and may be present from a variety of causes other than Addison's disease.

The prognosis of the disease is grave. Its course may be rapid leading to death in a few weeks or even days, or it may be prolonged from 6 to 10 years. Rarely complete recovery has been reported, due supposedly to regeneration of adrenal tissue.

The treatment is largely symptomatic, being directed both to relieving the more acute symptoms and to building up the general health by the ordinary well-known methods. In the latter connection it should be borne in mind that the great majority of cases are tubercular. Although organotherapy has distinctly improved the statistic as to cure or amelioration, it is by no means unfailing. In 120 cases collected by Sajous, 25 were cured and 36 improved. Either the desiccated gland (0.3 to 1.3 gm. t.i.d.) or hashed fresh gland given raw or boiled in meat foods may be utilized. In view of the probability that the chromaffin tissue is not essentially at fault the use of adrenin alone is not indicated.

Based largely on the obsolete "tonus theory" of adrenal physiology, an extensive literature has accumulated on the significance of the adrenals in states of general adynamia, especially those associated with infectious diseases. That such diseases may result in adrenal depression is probable, and, in fact, there is some specific evidence that such is the case. In these conditions adrenal organotherapy is frequently recommended. Neither its actual value, however, nor the precise indications for its use are well established.

The most significant information we have as to the function of the adrenal cortex is that tumors thereof lead to remarkable sex anomalies, the syndrôme génito-surrénale of the French. This may take the form of pseudohermaphroditism in females who have normal internal genitalia but whose external genitalia, body conformation, voice and psychic attributes approach the male type. Pubertas precox also belongs in this category, as do also adult virilismus and hirsutismus. These conditions are treated in another section (p. 745).

From such data it appears that the adrenal cortex has some sort of intimate connection with the sexual apparatus, a conclusion that is further borne out by the fact that cortical hypertrophy occurs during rutting, menstruation, lactation and pregnancy. The essential nature of the relationship is quite unknown. In any case it is not one of vicarious functioning since neither the adrenal cortex nor the gonads can replace the functions of each other in case of adrenal extirpation or of castration.

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CHAPTER XCV

DISEASES OF THE LYMPH-NODES

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Embryology.—In order to understand the rôle of the lymph-nodes in the human economy and to appreciate how admirably their anatomic structure is adapted to the work they perform a superficial review of their embryology and development may be of interest. In the human fetus of 5.5. mm. lymphatics of the skin may be recognized. These after frequently anastomosing form channels which empty into the fetal lymph sacs. Those of the head, neck, arm and thorax run toward the jugular sac, and those of leg, hip and abdominal wall toward the groin and posterior sac. These lymph sacs and capillaries have much the same relation to the tissue spaces as has the blood vascular system. Both are foreign structures which grow into or invade the mesenchyme. The tissue spaces are no more a part of the lymphatic system than the blood vascular system. Fluid in the veins should be called blood, in the tissue spaces, plasma and in the lymphatics, lymph. The first stage in the development of the embryonic lymph-node is the formation of a plexus of lymph ducts in the primary lymph sacs such as the jugular. Bridges of connective tissue separate the vessels. Primary groups of glands such as the jugular-subclavian, the retroperitoneal, and the iliac develop from the original lymph sacs; while secondary groups develop around plexuses of peripheral vessels. The last to appear are those in the final capillary bed such as the lymph follicles of the intestine, the Eustachian tube and the middle ear.

After the formation of such a plexus, lymphocytes heap up in the connective tissue septa and the lymph follicle is formed, the first being in the fetus of 50 mm. Next, in what is the second stage, blood-vessels enter. Now the follicle consists of a network of lymph vessels between which lies the connective tissue containing in its interstices blood vessels surrounded by lymphocytes. Lastly the lymph capillaries become the lymph sinus of the mature gland.

Hemolymph-nodes are not found in the human fetus.

Structure of Lymphoid Tissue.—In the matured organism lymphoid tissue shows the same two constituents, (*a*) a supporting reticulum and (*b*) lymphoid cells contained in the meshes. The reticulum is modified connective tissue; the cells, exceedingly numerous and closely packed together, are characteristically lymphocytes. A further differentiation of lymphoid tissue is the simple lymph nodule. This is seldom over 2 mm. in diameter, and consists of irregularly

spherical or elliptical masses of lymphoid tissue bounded by a denser peripheral zone. Within the looser area in what is known as the germ center lymphoid cells in various stages of mitotic division give birth to new lymphocytes. There are no definite lymph channels but a generous network of capillary vessels. Intermediate in complexity between the nodule on the one hand, and the typical node on the other, are the Peyer's patches of the intestine and the faucial and pharyngeal tonsils, containing groups of simple nodules blended into a single organ; the component parts or follicles, however, only partly retaining their identity.

Interposed along the lymph vessels and usually imbedded in the fatty tissue, the lymph-nodes show still higher types of differentiation. They vary in size from a millet seed to a lima bean or even larger, and occur either singly or in chains of from 3 to 10. Each one is surrounded by a capsule and from this trabeculæ penetrate the outer zone or cortex and divide it into pyramidal compartments of 0.5 to 1.00 mm. in diameter. In the cortex the lymphoid tissue appears as rounded nodules, while in the inner or medullary part it takes the shape of rounded cords. Germ centers are found only in the cortex.

Between the dense masses of lymphoid tissue and this trabecular framework lies a system of freely communicating channels, the lymph sinuses, through which flows the lymph brought by the afferent vessels. The sinuses thus are bounded on one side by the capsule or trabeculæ, and on the other by the gland pulp. The lumen of these channels is not absolutely free, but contains very delicate wide meshed reticulum which is continuous with the closer and more delicate network within the adjacent lymphoid tissue. Such an obstruction retards the passage of lymph through the nodes, and thus favors the entrance of young lymphocytes into the sluggishly circulating fluid.

Arteries enter and veins leave the gland at the hilum. The arteries follow the trabeculæ; then as they penetrate the gland substance proper where the connective tissue of the trabeculæ merges into the lymphoid tissue of the pulp, they break into capillaries which ramify in all directions. The afferent lymphatic vessels subdivide upon and in the tissue of the capsule and send branches to open into the lymph sinus of the cortex. The efferent lymphatics begin by vessels which lead from the lymph of the medulla and form at the hilum a dense plexus of tortuous lymph vessels. The sinus thus forms a path for the passage of lymph between the afferent and efferent vessels.

Both medullated and non-medullated nerves enter the node at the hilum. They are chiefly from the sympathetic system for the involuntary muscles of the blood-vessels and the capsule.

GROSS ANATOMIC RELATIONS OF THE LYMPHATIC SYSTEM

Lymph Vessels.—Before considering the individual groups of nodes in detail it might be of interest to glance at the circulation of lymph as a whole. Starting in the tiny, frequently anastomosing lymph capillaries of the peripheral parts of the body, the fluid slowly

works its way through the larger vessels to enter the general blood stream of the subclavian vein. The vessels of the lymph system closely resemble the veins, being related not only embryologically (lymphatics grow from the veins to the periphery) but also in that:

(*a*) They are supplied with valves.

(*b*) Their wall is structurally like the veins.

(*c*) Their fluid flows toward the heart.

They are dissimilar in that the terminal branches are closed, the present conception being that they end blindly in the tissue spaces. There is undoubtedly an interchange of contents, but this is through a closed membrane. Furthermore they are of greater caliber, being of 0.03 to 0.06 mm., whereas the blood vessels may be as minute as 0.008 mm. They do not increase regularly in size either, but the larger and smaller stems are indefinitely interspersed. The lymph vessels like many of the veins empty into the subclavian vein. Indeed they often accompany the veins and like them are grouped into superficial and deep sets. But they do not increase progressively in size as do the veins nor do they anastomose so frequently. They empty into two main trunks which discharge respectively into the right and left subclavian vein. The left trunk known as the thoracic duct is much the larger and traverses the whole thorax. It extends from the lower border of the second lumbar vertebra through the thorax on the left to the subclavian vein, and is the terminal of practically all the lymph channels of the entire body.

Lymph-nodes.—Nodes of the Head and Neck.—This group surrounding the neck like a collar, and dropping down a chain under each sternomastoid to join the nodes of the thorax, is of greatest interest to the pediatrician. Involvement of these nodes constitutes easily the highest proportion of glandular swellings in children. A knowledge of the anatomic relations is therefore of no little importance.

The nodes of the head—those which form the collar—are divided for the sake of convenience into different groups, namely: The occipital, the posterior auricular, the anterior auricular, the parotid, the submaxillary, the submental, the facial, the lingual, and the retropharyngeal.

The occipital nodes one to three in number lie immediately lateral to the trapezius. Their afferents drain parts of the scalp.

The posterior auriculars, roughly two in number, are located at the mastoid insertion of the sternomastoid muscle. They also drain areas of the scalp.

The one to three anterior auriculars lie in front of the tragus beneath the parotid fascia. They drain parts of the pinna, the external auditory meatus, and the skin of the temporal region.

The parotid glands are quite numerous and lie in the substance of the salivary gland. Their relations are similar to the anterior auriculars.

The submaxillaries in a chain of 3 to 10 follow the lower border of the horizontal ramus of the mandible. A large node lying on the facial

artery is most constant. Occasionally they are found right in the substance of the salivary gland. Their afferents drain the submental and facial nodes, and the adjacent tissues.

The submental nodes lie between the anterior bellies of the digastric muscle, and drain the skin of the lower lip and the floor of the mouth.

The facials are of no great clinical importance. Neither are the linguals.

The retropharyngeal group while small is of considerable clinical importance. Due to the small number of glands and to the difficulty in examining them pathologic processes are frequently overlooked while changes in the more superficial glands are clearly evident. They appear only as slight enlargements of the lymphatics in the posterior pharynx In addition one or two larger ones occur at the junction of the lateral and posterior surfaces of the pharynx about on a level with the anterior arch of the atlas. Imbedded in the fascia, they drain the pharynx and mucous membrane of the nose.

All these glands are closely connected by innumerable anastomoses of the lymph capillaries and all discharge their lymph into the deep cervical nodes.

Cervical Lymph-nodes.—While a superficial chain follows the jugular vein, the principal group is the jugular plexus extending down either side of the neck, and communicating with the groups of the thorax.

For description these nodes are divided into two divisions, the superior and the inferior deep cervical glands. The superior group about the bifurcation of the common carotid lies partly beneath the posterior edge of the sternomastoid and projects into the posterior triangle. It consists of 10 to 16 nodes. The afferents are of two classes. Some come directly from the glands of the head as the occipital, the submaxillary and other groups, while others come directly from the areas drained by these glands.

The inferior group lies near the lower border of the internal jugular and the subclavian veins, beneath the sternomastoid, and in the supraclavicular triangle. This group is continuous externally with the subclavian and axillary, and internally with the mediastinal nodes. It drains the superior nodes and also receives many independent stems from the adjacent tissues, even as far as the scalp, the upper pectoral region and the axillary nodes. The latter efferents unite with those of the deep cervicals to form the jugular trunk, which on the left opens into the thoracic duct, and the right unites with the subclavian trunk to form the right lymphatic duct.

All these deep glands lie in or beneath the deep fascia and so receive the efferent vessels of the superficial nodes as well.

Lymph-nodes of the Upper Extremity.—These are of little importance in children. The 16 to 36 lying in the axillary space drain not only the whole arm but also the anterior and lateral thoracic wall. Of the superficial brachial nodes the epitrochlears are the most constant.

Lymph-nodes of the Thorax.—These may be classified into two groups: (*a*) The parietal glands which are distributed along the internal mammary and intercostal arteries, and (*b*) the visceral glands. As the latter have come to be of such special interest to the pediatrician it is well to remember that they are subdivided into three main classes:

1. The anterior mediastinal nodes;
2. The posterior mediastinal nodes; and
3. The bronchial nodes.

These latter occur in several plexuses, namely, 7 to 10 lying on either side of the lower border of the trachea, and 10 to 12 lying in the angle between the bronchi.

Those beneath the right bronchus are the larger.

The pulmonary nodes are small and lie in the hilum of the lungs, between the larger divisions of the bronchi.

These nodes drain the lungs, the lower trachea, the bronchi, the heart, post mediastinum and send efferents to the thoracic duct or the subclavian vein.

Lymph-nodes of the Abdomen.—Excluding many unimportant ones there are several large groups: The celiac nodes numbering 16 to 20 lie in front of the abdominal aorta around the origin of the celiac axis and the superior mesenteric artery. The 20 to 30 lumbar nodes follow the abdominal aorta from the level of the second vertebra to the bifurcation of the aorta. Visceral nodes follow the principal branches of the aorta, and the 100 to 200 mesenteric nodes follow the superior mesenteric artery and its branches. In the pelvis many parallel the iliac veins.

Lymph-nodes of the Lower Extremity.—The only plexus of any importance is the inguinal group consisting of 12 to 20 glands lying in the inguinal region over Scarpa's triangle. They drain practically the whole lower extremity.

Hemolymph-nodes.—These are found especially in the prevertebral region of the abdomen. They resemble lymph-nodes, but are deepred instead of pink. Some consider them accessory spleens. Others hold them as lymph-nodes especially rich in blood supply, for transitional forms between them are believed to exist.

PHYSIOLOGY OF THE LYMPH-NODES

Lymph glands are primarily factories of lymphocytes; and their activity is constant as evidenced by the numerous mitoses seen especially in the germ centers. As the newly formed corpuscles accumulate in the middle of the follicle they push out into the lymph sinus lymphocytes already formed. Thus efferent lymph is richer in lymphocytes than afferent.

In the infant the glandular system is particularly active. We see this clinically by greater leukocytosis than in the adult. Again, glandular enlargements in the infectious diseases such as measles and scarlet

fever are marked, as is also the adenopathy of tuberculosis and syphilis. The microscope confirms these clinical observations by showing many germinative centers and much cell division. This offers perhaps an explanation for the more frequent lymphatic involvement in the child, for a general law of pathology shows that bacteria select the more rapidly growing tissues.

In addition to this physiologic function the lymph-nodes are of utmost importance as a line of defense against disease. A simple review of their microscopic anatomy and embryology reveals how beautifully adapted they are to filtering microscopic virus out of the system. Of course, their relation to disease has long been known, particularly the fact that just during or after the death period they are invaded by microörganisms. Experimentally their filtering property has been proved by injecting subcutaneously certain organisms, and then by culture recovering these very same organisms from the draining lymph-nodes. Diseases such as tuberculosis are known to produce characteristic changes. But more recent studies, both experimental and clinical, impress us more and more with the ever increasing importance of the protective action of these tiny organs. An interesting experiment is to inoculate a guinea pig subcutaneously with a non-lethal dose of staphylococci. A rapid tumefaction of the draining glands folows. Within three-quarters of an hour they become congested and filled with phagocytes brought by the lymph and blood-vessels. Then the polynuclears aided by the cells of the reticulum take up the germs. This is the picture when the node has had time for defense, i.e., hemorrhages, dense masses of polynuclears; and in some diseases such as diphtheria, even areas of necrosis. During this period the formation of new lymphocytes is not disturbed. Other typical experiments are those which show intravascular injection of certain organisms to be fatal; while the subcutaneous injection of the very same organism is harmless, these germs being removed by the lymph-nodes. Again, if one injects a guinea pig with a pure culture of diphtheria bacilli the glands necrose at once showing no defensive reaction whatsoever, and the animal succumbs rapidly. But if simultaneously diphtheria antitoxin is injected thus neutralizing the toxin, and giving the glands a chance for their lives, they react with intensive defensive changes, the infection does not pass and the animal survives. Thus in only the most virulent types of sepsis do the germs pass right through the nodes without, producing local changes and enter the blood stream.

Microscopic examination of the glands of these experimentally infected animals shows the bacteria lying more at the periphery than at the center. They are not so numerous in the sinuses and only rarely in the cords. Their stay when not ending in their destruction is accompanied by a diminution of virulence as has been demonstrated for the organisms of pneumonia, typhoid, tuberculosis and ordinary staphylococci and streptococci. Indeed some of these may remain quiescent for years, the present idea being that many cases of pulmon-

ary tuberculosis in the adult can be traced back to the original bronchial gland infection of the child.

Recent clinic observations have more than substantiated these experimental observations. The announcement of Bunting and Yates of the isolation from the lymph-nodes of the etiologic bacteria of Hodgkin's disease, of course, stimulated innumerable studies. To enumerate all these valuable researches is not necessary. Suffice it to say that in the last few years, hosts of observers all working with extreme care have arrived at the same conclusions. In a normal individual the nodes may harbor great varieties of bacteria, held in captivity apparently as harmless saprophytes producing no clinical symptoms whatsoever. Streptococci, staphylococci, gas-bacilli, pleomorphic bacilli, all have been reported not only in glands removed from individuals suffering from great varieties of ailments, but even in glands removed experimentally from normal individuals. At present it seems that the discovery of the diphtheroid organism is not of so much importance as regards its relation to Hodgkin's disease as it is in elevating, by the studies stimulated, the physiology of the lymph-nodes to a much more dignified position in the human economy.

Some diseases such as tuberculosis and plague seem to pick out the nodes as primary points of attack. If we inject tubercle bacilli into the blood stream we often find them localizing in the lymph-nodes. Whether they have specifically picked out the lymphatic glands or have been specifically filtered out is still an open question.

From the above it would be logical to consider all glandular enlargements as efforts of the body to defend itself against infection and with such a viewpoint adenopathy in itself should not be considered a danger sign. It is simply a phenomenon associated with infection. Thus therapeutically we should do everything in our power to aid the glands in their work and certainly not handicap them.

CLINICAL SIGNIFICANCE OF ENLARGED LYMPH-NODES

In discussing the importance of enlarged lymph-nodes it may be well first to say just a word as to the technique of examination which is much the same as in adults. The routine should be definite and systematic. Using both hands, examine bilaterally and simultaneously the occipital, posterior auricular, and cervical nodes. Then pass to the axillary using the right fingers for the left axilla and *vice versa*. Next come the cubitals, and then the inguinals. Lastly the writer seeks evidence of intercostal adenopathy and bronchial gland enlargement. In seeking the cervical glands the head should be drawn slightly forward, and the muscles of the jaw and neck relaxed. Due to the small size of the child's muscles the cubital glands may offer some difficulty, and this is increased during a fit of temper or fear. The writer finds the following technique simplest: Doing everything possible not to frighten him, lay the child on his back with the arms to the side. With the right hand grasp the patient's right hand

and raise the lower arm until perpendicular to the table. This relaxes the muscles of the arm, and then the observer's left first and second fingers easily feel their way into the bicipital groove. Palpation should be very gentle. Use just the same pressure as if trying to palpate something directly beneath the skin. The lighter the pressure the more easily will the nodes be felt. In order to avoid the brachial nodes which may be misleading, do not palpate above the lower third of the arm. These cubital nodes are fixed but loosely in the subcutaneous tissues and may not be found at the very first touch, but if one persists for a few moments it is surprising how frequently they become evident.

The axillary nodes are often present and frequently overlooked. The shoulder should be relaxed; the arms placed absolutely parallel to the sides of the body. Palpation gentle but high in the axilla locates them.

The intercostal nodes are of considerable interest because they are the only nodes which can be seen better than felt, and because they have been described as pathognomonic of pulmonary tuberculosis. Particularly is this the view in Vienna. To locate them place the child upon his side and extend the arm well above the head. Tiny pea-sized enlargements protrude from the intercostal spaces below the axilla. In a considerable series of cases in this country the writer has done a von Pirquet test on all children showing these glands. Practically all have been negative. The conclusion is self-evident. Undoubtedly in many conditions other than pulmonary tuberculosis the intercostal nodes enlarge. Why this discrepancy in our observations is, of course, open to speculation. Perhaps in Vienna the percentage of tuberculosis is so tremendously high that the association with such nodes is purely incidental.

The identification of enlarged bronchial lymph-nodes is not easy and often impossible. Clinicians have devised various methods, the most satisfactory being the following two: First, starting in the lower thoracic region and using the middle finger percuss directly upon the spines of the vertebræ upward to the cervical region. Normally there is gradually and slowly increasing dulness from below to marked dulness in the cervical region. In cases of bronchial adenopathy dulness may begin on a level with or below the middle of the scapula. Second, auscultate over this region. Normally bronchial breathing does not begin below the cervical region, but in positive cases it will be recognized at the level of the middle of the scapula.

Clinicians have come to recognize, however, that these signs are by no means infallible. Only those glands which when enlarged press directly backwards into the posterior mediastinum give the above findings—the fluoroscope or roentgenogram may disclose those enlarging in other directions. Great stress is laid upon these glands, as many consider their enlargement practically pathognomonic of tuberculosis in the child. But we know also that they are involved in many other pulmonary infections. After all, when the von Pirquet test is so simple

and so reliable in young children, demonstration of these nodes will be of more value from the viewpoint of pathology and prognosis than of diagnosis.

The physician while examining the child should never neglect the occipital and posterior auricular nodes. They take on singular significance in children, for their enlargement not only points to typical scalp lesions such as pediculosis, eczema and ring-worm, but is an important prodrome of German measles. Often before the occurrence of subjective symptoms or even a trace of a rash the fingers of the observer feeling these hazel-nut sized enlargements warn of an approaching attack of this ailment.

Some claim that enlarged nodes are not easily palpated in fat infants. This is not an important factor. An appreciable increase in fat only rarely occurs before the second year. Then again fat children being usually healthy have fewer glandular enlargements. To settle the point observers have compared the weight of the child to the number of palpable nodes and found absolutely no relation.

Given a case of lymph adenopathy one is confronted with the questions:

(*a*) Is this simply a part of a general sepsis?

(*b*) Is this secondary to a focus of infection in some other part of the body?

(*c*) Is this a primary affection of the node?

Before going into the problem, however, one should have a pretty general knowledge of those enlargements we are accustomed to call "normal," for practically all healthy children show some palpable nodes. Children of two years having been relatively only slightly exposed to infection make the best material for study. Several of such investigations have been made, a typical example being the work of Coerper (1915). In a large number of healthy children including 100 newborns he examined with great care 11 groups of glands, the occipital, auricular, cervical, mandibular, submental, supraclavicular, cubital, brachial, axillary, pectoral and inguinal. Of the 100 newborns, only five had no palpable nodes, these being seven month prematures. Of the remaining 95, all had axillaries, while many had cervicals, inguinals and occipitals. Only 46 had axillaries exclusively after the third day. The cause of the preponderance of axillary involvement lies probably in the physiologic breast swelling of the newborn.

The number of palpable nodes increases steadily from birth. Next to the axillaries come the cervicals, for probably the first infections enter through the naso-pharynx. Interestingly enough and showing the unusual susceptibility of the lymphoid apparatus in the child, is the observation that this cervical swelling occurs coincidentally with all the other manifestions of the infection. In 17 cases inguinal glands were felt. In some, these seemed related to disturbances of the navel while in others they seemed part of a general infection as a coryza.

Children with three or more glands at birth were definitely injured, *i.e.*, showed trauma, skin infections or forceps lesions, while those with subcutaneous hemorrhages showed even more adenopathy. Jensen in another study goes even further—24 of his 240 cases showed cervical nodes immediately at birth and 50 after two to seven days. He concludes that glandular swelling does not necessarily come from exogenous infection, for even some of his cases delivered by cesarean section showed cervical nodes. Forty-three per cent. of his newborns showed palpable cervicals; while in Coerper's series these did not develop until the third to fifth day.

It is of particular interest to note that in no newborn was any general adenopathy found. Thus the much discussed lymphatic constitution can scarcely be a congenital anatomical pathologic entity. Apparently the diagnosis can only be established by a functional test, namely, the reaction of the lymph system to exogenous injury.

The general glandular history of an infant is as follows: A baby born with one palpable node by the end of the first month will show two; by the end of the third month, three, and by the end of the tenth month, four. The number is of course influenced by the child's immunity to disease and the number of times it has been exposed to infection. Children with increased immunity, i.e., those on breast milk show fewest glands. The difference between the normally and the artificially fed is striking, the former having one-seventh as many palpable nodes as the former. Those breast fed children showing within the first few months any considerable adenopathy have been raised in poverty and poor hygiene.

Thus we learn that a few nodes are practically always present, and unless recently enlarged or associated with definite symtomatology are of no clinical importance. These studies also showed that the consistency of the node is not of much significance, for many normal children have nodes of the firm indurated type usually ascribed to lues.

Glandular Enlargements Associated with General Infections.—To enumerate all the diseases associated with glandular swelling would be to write a textbook of medicine. Suffice it to say that in all the exanthemata, in all cases of sepsis, in all infectious diseases from bacillary dysentery to trypanosomiasis changes will be found in the lymph-nodes. Indeed some organisms such as bacillus pestis seem to single outspecifically lymphoid tissue, and again in trypanosomiasis a drop of fluid aspirated from the glands will contain more organisms than are in the blood or in the cerebrospinal fluid.

Glandular enlargements are very characteristic of the exanthemata in childhood, but to diagnose any particular disease on the basis of such enlargement is not feasible. In practically all, the enlargement is general. It is, perhaps, greater in German measles than in measles; it is quite constant in scarlet and diphtheria. In the latter two the degree of cervical adenitis seems to depend upon the intensity of the throat involvement. The cervical adenopathy of measles is inclined to persist for some time and though suppuration is rare, tuberculosis

frequently follows. In German measles, on the other hand, the glands though often larger disappear more quickly. In vaccinia the glands are often involved on the side vaccinated, and during the period of anaphylaxis following the injection of horse serum the writer has found local adenopathy near the seat of the injection. As regards scarlet fever, the writer has had a rather interesting experience: In Vienna during the routine examination of several hundred scarlet fever patients he found enlarged cubital glands invariably present, and came to look upon these as important factors in the differential diagnosis. Continuing the observations in this country, however, he found the epitrochlears only seldom present. Why this difference? Perhaps the explanation is the same as that advanced above in discussing intercostal adenopathy and tuberculosis. In Vienna probably the high degree of tuberculous involvement and the great frequency of all glandular enlargements led the writer to ascribe as cause and effect two conditions which were coincident but not related.

The so-called disturbances of nutrition seem associated with special adenopathy, the severer types showing three times as many nodes as the milder ones. This is of importance particularly from the prognostic side; the malnutrition baby with many glands has a severer disturbance than one with only a few. A beginning disturbance in a child with many glands is more serious than in one with fewer. In these severer disturbances it is an open question whether the adenopathy is due to coincidental bacterial infection or to endogenous toxins; perhaps both.

Rickets in itself does not give any glands until the complications of the second year. Eczema resembles disturbances of nutrition. The glands of dirt-eczema resolve quickly; those of a truly exudative child do not.

The glandular history of lues is interesting. The newborn may on the first day show one axillary gland; by the fourteenth he will have cervicals, occipitals, axillaries, and often cubitals. The latter, however, may not develop until the third month, coincidentally with the spleen. During these first three months the general number is not much increased over the normal and the glandular picture is much like that of disturbed nutrition. After the third month, however, the number doubles the average. These glands, nevertheless, may not all be luetic. Not only lues but also disturbed nutrition give cubital and even intercostal glands; so these can scarcely be considered pathognomonic of any one condition. The writer himself has found many palpable epitrochlear nodes in innumerable children who have not shown a trace of syphilitic infection. Probably the only nodes that may be considered as even highly suggestive of lues are those occurring bilaterally in a long chain high up in the bicipital groove.

Tuberculosis as a general disease, independent of any definite tuberculous adenitis contrary to general opinion does not give general adenopathy. Probably no glands unless specifically infected by the organisms will enlarge due to tuberculosis in another part of the body.

Any such enlargement will be found secondary to local infections as scrofulous skin changes or eczemas.

CLINICAL ANATOMIC CONSIDERATIONS

Enlargements Secondary to Local Foci of Infection.—Undoubtedly the great majority of glandular enlargements are secondary to some focus of infection in some other part of the body. Ideally, if we knew the location of the node and the area it drained it would be a simple matter to locate the focus. Unfortunately for the clinician, however, the complexity of the system and the innumerable anastomoses permit infections to spread, not only to the immediately adjacent glands but also to all those in the neighboring territory. Probably no one gland ever drains one certain anatomic region but pathogenic processes spring from group to group. Thus in any involvement of the scalp the infection spreads not only to the occipital but also to the posterior auricular, the parotid, the superficial cervicals; and may even reach the submaxillary nodes if the lesion is in the frontal region. The occipitals and auriculars also drain the naso-pharynx, and particularly the ear, for they enlarge very characteristically in mastoid disease.

The parotid glands are involved in lesions of the scalp, the outer lids, orbit, cheeks, naso-pharynx, external auditory meatus and typanum. Acute enlargements may be mistaken for mumps; chronic enlargements for tumors. Suppuration in these glands is very painful on account of the tense parotid fascia.

The submaxillary glands drain the middle portion of the forehead and face, the inner portion of the mouth, pharynx, tongue, gums, teeth, and the lower jaw. They are especially susceptible to pyogenic infections. Enlargement of a single node may be mistaken for a growth in the submaxillary gland itself.

Cervical glands constitute 50 per cent. of all palpable nodes in infancy. Their involvement points strongly to the naso-pharynx as the portal of entry. Interestingly enough in thrush the infection often misses the mandibular glands completely and goes directly to the cervicals. The superficial cervicals enlarge in superficial inflammations, the deep ones in a great variety of conditions as in eczema, wounds and ulcers of the face, dental caries and abscesses, pharyngeal, facial and tonsiller inflammations, otitis, etc. More rarely they are affected with lymphosarcoma or Hodgkin's disease. In affections of the tonsil and jaw one node particularly enlarges and projects in front of the sternomastoid about ½ in. below and somewhat internal to the angle of the jaw. As the lower deep cervicals enlarge following any disease of the upper ones, we find practically all superficial cranial lesions followed first by involvement of the respective group, then of the superficial cervicals, and then the deeper group.

The retropharyngeal glands lie in that space and communicate with the upper deep cervicals. They become infected through the

overlying mucosa as they are in close relation with the buccal portion of the pharynx which is rich in adenoid tissue. We shall discuss them in some detail later.

The arm-breast groups though anatomically separated are clinically united, for the pectorals and axillaries usually enlarge together.

The bronchial nodes, due to their relation to tuberculosis, take on a singular significance in childhood.

The inguinals are of no great clinical importance.

CLINICAL PICTURES COMMON TO CHILDHOOD

Cervical Adenitis.—This condition while almost invariably secondary to some focus of infection is of such importance in the field of pediatrics as to require special consideration. The child is acutely ill showing the fever, pulse beat, anorexia and malaise characteristic of an infection.

One or usually more of the deep cervicals are enlarged to hazel-nut or even walnut size. The enlargement usually remains discrete, but as the condition progresses the nodes may become matted together and even break down. The condition is, as a rule, painful and the little patient holds the head to one side to protect the diseased area as much as possible.

Diagnosis.—Receiving such a patient first obtain a careful history. Learn the duration of the condition. Many mothers will state that the glands have been enlarged for months, but careful questioning discloses that there has really been a succession of acute attacks with subsidence of the swelling between times.

If the glands have been consistently and chronically enlarged or are slowly but progressively enlarging, one must think of chronic cervical adenitis, tuberculosis, syphilis, and the rarer diseases such as leukemia, pseudoleukemia and tumors. On the other hand, if the condition is acute especially if associated with fever, in all probability the diagnosis is acute cervical adenitis.

Under such circumstances first seek the primary source of infection. In children we are placing increased stress upon diseased tonsils and adenoids as primary portals of entry. It might be well to add here parenthetically that adenoids are not organs which have just recently taken on pathologic properties from our newer modes of living. More probably their importance has only recently been realized. Stauffer interestingly calls attention to the portrait of Emperor Ferdinand I, of Germany, hanging in one of the galleries of Florence. The unknowing artist far back in the year 1524 faithfully depicts a typical adenoid facies. Adenoids produce most of their symptoms between the third and fifteenth year; the very years in which cervical adenitis is most frequent. But do not be misled entirely by just one idea. Often in older children a careful search will disclose the provocative factor elsewhere; in decayed teeth, pediculosis, infections of the scalp and ears, and last—but certainly not least—in retropharyngeal abscess.

Treatment.—The treatment must logically consist of caring for the enlarged glands themselves and equally as important of correcting or removing of the causative focus.

As regards actual treatment of the enlarged glands the writer is somewhat of a skeptic. All possible forms of ointments have been employed, the favorite being ichthyol. Many observers have objected to this, however, due to its unpleasant odor and dirty color. Others have recommended applications of tincture of iodin; some favor wet dressings of aluminum acetate. In view, however, of the etiology and pathology of the condition, the writer is inclined to doubt whether we should take very active steps at all. The glands are the first line of defense against a more general invasion of the body by infecting organisms. They are doing all in their power to filter out and destroy the disease germs. In each gland the resisting leukocytes and tissue cells are waging battle on the hostile bacteria. First then be sure that the treatment will be a definite aid in this struggle. For this reason unless using other agents as a placebo the writer prefers hot applications. Heat soothes the pain, does not chill the susceptible child, and is scientifically sound in that it attracts blood with the accompanying leukocytes and healing ferments to the part. Cold seems reasonable in just one condition, namely, when the gland is so engorged with blood that this in itself has cut off its own blood supply. Then, of course, cold will be more soothing to the pain and by relieving the congestion will restore better circulatory conditions.

Whether heat be applied in the form of hot-water bag, hot moist dressings, or a flaxseed poultice makes little difference. The poultices are perhaps more convenient to adjust and retain their heat longer than the moist dressing. Many observers and writers of textbooks warn that heat is more likely to cause abscess formation than cold. This the writer is not prepared to admit. He has seen many, many glands resolve under hot applications, and even if occasionally suppuration does result, perhaps this is of more value to the general human economy than if the glands had been spared, but the organisms allowed to enter the general system.

If, as is usually the case, the infection is overcome without pus formation some weeks will elapse before the glands resume their normal size. Such is required for resolution and during this do not interfere with normal processes. Advise the parents in advance what to expect.

If the glands break down one should urge against too early incision. There is, of course, a general law in surgery that wherever pus is present it should be drained, but unpleasant after-results sometimes follow the application of this principle. It must be self-evident that where all glands are fighting actively against the disease some will break down earlier, some later. Too early incision only means that either a disagreeable sinus will result, or that other incisions may be necessary later. As indication for surgical intervention the writer is not guided entirely by the temperature. Fever only shows that the battle is

going on. It is better to let the index be the patient's general condition. When this is good and the child bears the infection satisfactorily, even if slight fluctuation be palpable, the writer prefers in spite of high temperature to wait until he is sure that all the doomed glands have broken down entirely. Then a small incision releases the pus, and the wound heals rapidly with no disagreeable after-effects.

The treatment of the primary focus as soon as feasible is simply its correction or removal. If tonsils or adenoids be the factor, however, *under no circumstances* remove them while the disease is acute. The large expanse of injured tissues, severed blood-vessels, and torn lymphatics exposed to invasion by the still virulent organisms offers an inviting entrance into the system itself. Many a fatal septicemia has resulted from too hasty removal of tonsils and adenoids. Under no circumstances should they be touched while acutely inflamed.

Chronic Cervical Adenitis.—When not due to definite glandular disease as tuberculosis, syphilis, Hodgkin's, tumors, etc., chronic cervical gland enlargement usually results from repeated acute attacks. In the latter case while treatment of the glands themselves will be of little avail, removal of the tonsil or adenoid or whatever the etiologic factor may be is curative.

There is one type of chronic cervical gland enlargement which is frequently confused with tuberculosis. The child is a typical mouth-breather, pale, weakly, with poor physique, and long narrow chest. Ordinarily he is described as of "tuberculous diathesis," or by the Europeans as "habitus asthenicius;" or again the wise men speak of "lymphatic constitution." Abnormalities of posture give rise to areas of dulness on percussion. Before the days of the von Pirquet test these children were universally considered tuberculous. More recent studies, however, have shown this not so. Fluoroscopic examination of the lungs melts the dulness away and the von Pirquet test is invariably negative. While these children seem constitutionally pre-disposed to enlarged glands, tonsils and, even more, adenoids probably play a greater part in the preponderance of the cervical enlargements.

Tuberculosis of the Lymph-nodes.—To take up the subject of glandular tuberculosis in all its aspects would be too extensive for the present article. Suffice it to say that *clinically* the most frequent glandular tuberculosis in children is the cervical. Up to the present most of the work in this field has been done by the surgeons. In their descriptions, particularly with a viewpoint as to feasibility of operation, they have divided the cases into three distinct groups:

(*a*) Those in which the infection seems to have entered through the tonsils and air passages, passing from there to the upper cervical glands.

(*b*) Those where the disease has spread along the jugular chain and sinuses are formed.

(*c*) Those cases of diffuse tuberculosis with other foci scattered throughout the body.

In the first group the surgeons claim very beneficial results by careful dissection of the involved glands. In the second the results are not so satisfactory, and in the third they are still less favorable.

In the clinics of our surgical colleagues the above classification doubtless holds very true, but from the viewpoint of the pediatrician it is almost valueless. These cases have been seen too late. Children with generalized tuberculosis, children with universal glandular enlargement and with discharging sinuses have been suffering from improper treatment, poor care, and great neglect. What the pediatrician must insist upon is an early diagnosis, a diagnosis when there is only slight involvement and when chances for recovery without any surgical intervention whatsoever are good.

Our present attitude, based largely upon the extensive and splendid studies of Ghon and his associates, must be that in children all cases of tuberculosis really belong to the third type. We believe now that in infancy the tubercle bacillus is first inhaled into the lungs, usually the right lower lobe. There it forms a tiny focus and then travels rapidly by way of the lymphatics to the bronchial lymph-nodes. These enlarge, producing symptoms both of tuberculosis and secondary ones of pressure. From here the disease may spread to the lungs, may involve the cervical and other lymph-nodes, or may remain absolutely quiescent to take on activity during later years. The writer does not mean to insist that children can be attacked only in this way. Undoubtedly the disease may spread by way of the tonsils and upper air passages. Undoubtedly some cases develop from infected food with the primary focus in the mesenteric lymph-nodes, but the writer feels justified in stating that the present tendency is to regard inhalation as by far the most frequent source of infection.

Diagnosis.—With a determination then of making an early diagnosis we must gaze upon every case of cervical gland enlargement as one of possible tuberculosis, and in these cases whenever the family history, the child's past history and environment, or the child's symptoms suggest tuberculous infection we must do a von Pirquet test. With positive history and definite glandular enlargement, a positive von Pirquet, particularly in early childhood, is of very great significance. Although in justice to ourselves and to our child we should always consider tuberculosis seriously, it is surprising in how relatively few cases in dispensary work in Chicago the test will be positive compared to the large number of enlarged glands due to tonsil and adenoid infection.

As regards the diagnosis from the clinic standpoint these children have all the typical reactions of tuberculosis: Loss of appetite, and as the disease progresses loss of weight, emaciation, night-sweats, and evening temperature. The glands at first remain discrete, refuse to gather, and form knotted masses covered with edematous skin. Suppuration eventually occurs. Occasionally the symptoms may be due to other diseases primarily involving the lymph-nodes such as Hodgkin's, or even tumors, and at times a diagnosis cannot be made without microscopic examination of a resected gland.

But the writer wishes to urge most seriously that if the condition were tuberculous it should never have reached this stage; it should have been diagnosed almost at the stage of primary involvement and to do this is relatively simple if one will only upon slightest provocation employ the von Pirquet test.

Treatment.—If an early diagnosis has been made it will be seen that hasty removal of the gland is illogical. This was at first, of course, advised with the hope of completely eradicating the disease. Now we consider this impossible. The primary infecting germs are always far beyond the reach of the surgeons's knife. A complete resection causes severe shock to the child, opens up the lymphatics, releases germs that have been already imprisoned thus helping spread the disease, but does not touch the primary focus in the bronchial lymph-nodes. The general treatment of tuberculosis is really the most satisfactory for these early cases. Remove the child from his tuberculous environment, give him fresh air, sunshine, and good food. For medication cod-liver oil and the syrup of the iodid of iron are highly recommended. In regard to general treatment the writer will never forget Dr. Rollier and his beautiful sanatarium in Leysin, Switzerland. It was Rollier who first discovered (or at any rate first to any extent (applied) the effects of the sun's rays in curing the tuberculosis of childhood. He located his sanitarium at an altitude of 5000 ft. on a beautiful mountain peak. At this height, though the sun's rays are appreciably warm, the air from the surrounding snows is cool, crisp, and refreshing. At this altitude the child's whole body can be completely exposed to the sunlight, the rays being bright, penetrating, and warm while the pleasantly cool air prevents any undue burning. Such a happy combination can only be obtained at these elevations. It is no uncommon sight to see a crowd of little ones, clothed only in trunks, snow-shoeing merrily over the snow fields. The treatment consists simply in exposing the diseased parts to the sunlight. The cures have been remarkable.

This treatment was first applied to diseased bones and joints, such cases which under the surgeon's knife are eventually cured but leave the unfortunate child deformed and a cripple. Under the sunlight treatment of Leysin these lesions melt away and not only is the disease cured, but still more remarkable the little one retains the use of his limb and suffers no cruel deformity. How strange it is that this country has not made more use of these splendid studies of Rollier!

The sunlight treatment can be applied to all other forms of tuberculosis and certainly to the glandular type. The success of the treatment lies in the good food and hygiene offered the child, and in the continuous and prolonged application of the sun's rays. True, considerable time is necessary, often a year; but a happy healthy child perfectly normal in every way and with no deforming scars is the pleasant result.

The local treatment consists in applying various salves, ointments and tincture of iodin, all of which with perhaps the exception of the iodin the writer believes of little value. In our lower altitudes where

the great heat of the sun makes prolonged exposure unbearable much can be accomplished with the Roentgen-rays. More and more are these finding their place in the treatment of tuberculous adenitis. Trained radiographers in large series of cases claim excellent results, their treatment, however, lasting sometimes two years, with applications every three weeks. Strange to say the Roentgen-rays are more efficacious in those glands which have broken down, become caseous, and given rise in fistulæ. The simpler types respond just as well to general treatment, hygiene, fresh air, and sunlight. In abscess formation where no fistulæ have formed the most satisfactory treatment is to aspirate the fluid under the strictest asepsis and then apply the rays to the tissue remaining.

As regards the technique the rays must be hard and filtered. How they produce their effect is uncertain, but at any rate they can reach more tissue than does the surgeon's knife for usually many more glands are diseased than clinical evidence indicates. Perhaps by the destruction of tuberculous tissue vaccines are freed. It has been observed that following *x*-ray treatment of a lesion in one part of the body other tuberculous foci heal, and there may be general systemic improvement. Locally the diseased glands seem less resistant to the rays than the surrounding tissues and react with fibrous degeneration. The lymph-vessels become fibrous cords and this in itself may be an important factor in preventing the spread of the infection.

Affections of Nodes Other than the Cervical.—Although in children adenopathy is most frequent in the cervical region there is no reason why any node may not be involved. Like the cervical glands the node usually enlarges in response to an infection elsewhere. After ruling out the primary diseases of lymphoid tissue as Hodgkin's or leukemia, and conditions as tuberculosis and syphilis, the physician must search carefully for the primary focus. This may often be obscure as, for instance, in infections of the eyelids, in subacute infections of the middle ear and mastoid, or in frost bites and irritations of the skin. A not infrequent cause of axillary adenitis is an infected hang-nail. Some observers believe that axillary adenitis may even have its origin in affections of the eye for it has been ascertained in experiment that if the conjunctiva of a dog be rubbed with a culture of tubercle bacilli cervical adenitis may follow while the eye remains normal. To show how conscientious one must be in the search for a primary focus the writer quotes a case of Dr. D. C. Straus: The patient, a little boy of two years, was brought for inguinal adenitis. He had been treated by various physicians with local applications as no primary focus on his foot was apparent. More thorough examination revealed an ischio-rectal abscess. The proper draining of this resulted in the prompt healing of the adenitis.

While the lymph-nodes of the abdomen are not readily discernible clinically, it is well to remember that the celiac nodes are readily involved in diseases of the stomach and other viscera, and the mesenteric nodes enlarge in typhoid, in peritoneal and intestinal tuberculosis.

They are also involved in any condition causing diffuse adenopathy, and in leukemia or Hodgkin's disease reach surprising size. Indeed, abdominal forms of the latter may show very little in the superficial nodes and marked findings in the deeper ones of the abdomen.

Associated Symptoms Due to Glandular Enlargement.—Besides the symptoms due to general infection, or due to a specific disease, some glandular swellings are of great practical importance because of the pressure upon adjacent tissues. Thus enlarged occipital nodes by pressing upon the occipital nerve may cause considerable pain. Imbedded in the parotid gland about on a level with the upper extremity of the tonsil lies a small lymph-node which at times enlarges in tonsillar infection. The pain due to pressure on the tense parotid fascia may simulate an otitis media. A small gland is located just above the middle of the thyroid cartilage of the larynx. When enlarged it presses upon the superior laryngeal nerve and causes pain on deglutition, ascribed by the patient to his pharynx. Another gland lies under the sternomastoid muscle just against the inferior cornua of the thyroid cartilage, and by pressure on the recurrent laryngeal nerve may prevent perfect approximation of the cords. This is a more frequent cause of hoarseness than inflammation of the cords themselves. The usual cervical adenopathy of tonsillar infection rarely causes any pressure symptoms except when very rarely a deeper node may press upon the vagus.

In discussing tuberculosis we spoke of the importance of the bronchial glands as one of the first points attacked. When involved to any extent they produce a very definite clinical picture, *i.e.*, one of definite mediastinal tumor. In addition to the usual symptoms of tuberculosis these children suffer from definite pressure symptoms. They show expiratory dyspnea, a harsh barking cough, occasionally symptoms from pressure on the recurrent laryngeal nerve, and, of course, the physical signs and fluoroscopic shadows typical to mediastinal tumors. With no other clinic symptoms present, upon hearing this metallic barking cough in an infant the physician should always consider tuberculosis. Fortunately with the von Pirquet test we can now diagnose the disease long before it has developed to such a stage.

Retropharyngeal Abscess.—One condition typical to childhood in which the severity of the local symptoms are much greater than the virulence of the infection would justify is *retropharyngeal abscess.*

The retropharyngeal glands lie in that space and communicate with the deep cervicals. They become infected through the overlying mucosa as they are in close relation with the buccal portion of the pharynx which is rich in adenoid tissue. If suppuration occurs a fluctuating swelling pushes this portion of the pharynx forward (the connective tissue being rather lax), depresses the soft palate and causes dysphagia. If the abscess is lower aphonia and dyspnea result.

In the early stages the diagnosis is not easy. Local symptoms may for a time be absent. The child shows fever, loss of appetite, peevishness, restlessness and general symptoms common to all infections.

Later when the abscess has developed, fever becomes higher and the child sicker. The posture is typical. Lying with head drawn back, with loud gurgling respirations and retraction of the interspaces, the child suffers from all the agony of severe respiratory obstruction. Failure of the physician to recognize the abscess may result in death from asphyxia, or by gravitation of the pus downward along the esophagus to the mediastinum. Again a sudden rupture into the

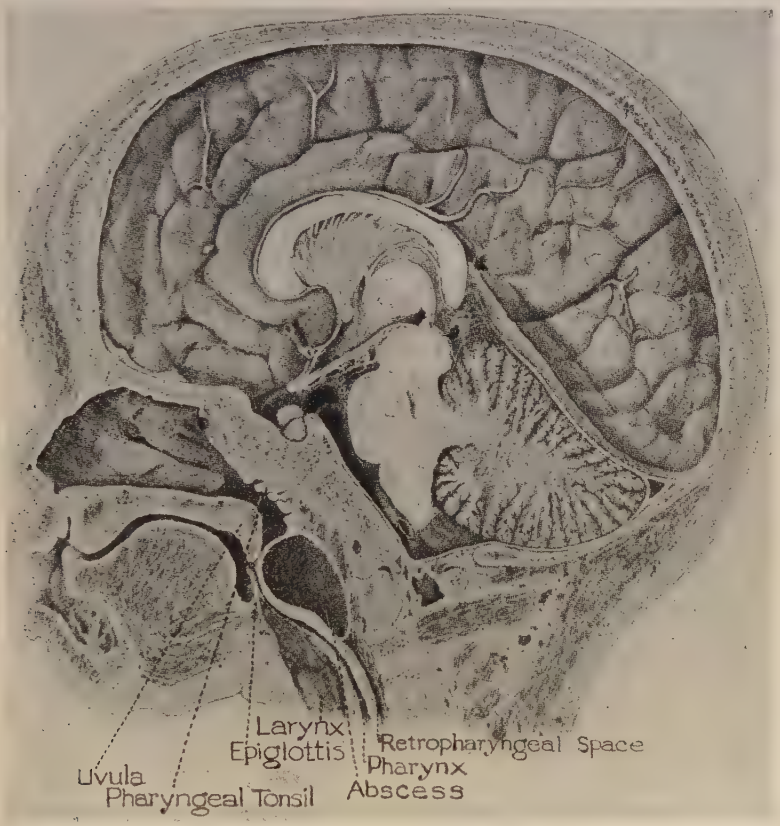

FIG. 156.—Retropharyngeal abscess (Calvin C. Rush, in Jour. Am. Med. Assoc.).

pharynx may lead to pneumonia by aspiration. Even when quite large the abscess may not be visible on examination because of edema of the soft tissues. But it may be palpated. The writer urges that in all cases of obscure fever where any suggestion of the above symptoms are present never to neglect very careful—but very gentle—digital exploration of the pharynx.

Pfeiffer's Glandular Fever.—Occurring in epidemic form with sudden onset, cervical adenopathy, and temperature up to 105°F., Pfeiffer's glandular fever is no longer considered a specific glandular disease. Its typical symptomatology was described in 1889, but since

Trautman in 1904 argued against this it is considered the usual form of grippal infection associated with rather marked adenopathy. The onset is mostly in children of five to eight years of age with anorexia, joint pains, restlessness, and fever. The symptoms are largely naso-pharyngeal, i.e., red throat, coated tongue, dysphagia, rhinitis and inflammation of the upper respiratory passages. The children are all well in a few days. It is probably just a naso-pharyngitis in a lymphatic child.

As an argument against the non-specificity of the disease is the observation that during influenza epidemics while adults may show all the typical symptoms, many children will react with only fever and adenopathy. Again this disease occurs in school children during the winter months when repeated respiratory infections are so common. In the summer the children are free from disease.

Primary Diseases of the Lymph Glands.—Perhaps most hopeless of all tumors are those of the lymph-nodes. These resist even *x*-ray and radium. Operation is of value only when the site of the disease is isolated and this, of course, is difficult to diagnose clinically. Whether the various types of lymphatic tumors and diseases such as Hodgkin's are related is perhaps still open to some discussion. At times histologic examination is confusing and in this respect the work of Maude Slye is of interest. For 10 years she worked with hereditary cancer in mice and was able to produce a breed in which almost every member died of cancer. In these cancer families different types of malignancy occurred, some showing carcinoma, others sarcoma, others epithelioma and others Hodgkin's disease or lymphatic leukemia. W. B. Coley uses this as an argument for the more general use of his mixed toxins of erysipelas and prodigiosus.

All types of tumors have been described and the diagnosis can only be made by blood examinations and often only by histologic study of the resected specimen. Tuberculosis has been shown to resemble malignant disease and Hodgkin's. Hodgkin's has been confused with spindle-celled sarcoma.

Primary endothelioma is probably more common than was previously thought.

So much confusion consists in the diagnosis and understanding of these so-called primary diseases, that it may be well to conclude by quoting the recent work of Symmen who believes that Hodgkin's disease is after all not a primary disease of the lymph-nodes, but one having its origin in the bone marrow.

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CHAPTER XCVI

METHODS OF ESTIMATING RENAL FUNCTION IN CHILDREN

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Undoubtedly the most delicate and certain means that we have of detecting an active pathologic process in the kidney is by examination of the urine for the presence of albumen, casts and cellular elements. While it is true that a single urine specimen may fail to show any of the pathologic elements, in the presence of an active nephritis one or more of the abnormal elements will always be discovered if repeated examinations are made. The value of a single examination, however, is strictly limited in that it offers but little help in determining whether the process is subsiding or progressing, and at what rate. It is important in considering prognosis and treatment to obtain definite information as to how much damage has been done, how fast the lesion is progressing, and which of the several excretory functions of the kidney is impaired; whether, for example, the chief difficulty lies in the excretion of solids or of water.

It was supposed by the earlier investigators that measurement of the selective excretory action of the kidney would locate definitely the anatomic lesion as seen by the pathologist. Such has not proved to be the case, and discrepancies between the forecast and the findings at autopsy have been found to be so frequent that it is now generally conceded that functional tests as yet offer us little help in that direction. It is hardly to be expected that in so complicated an organ as the kidney one structural element could be affected without impairing the action of other renal structures and so make it extremely difficult to determine the initial lesion.

Many tests for determining kidney function have been devised. Some were found to be inadequate and soon were discarded, while others, although of value, were too complicated or cumbersome for general use. Many of the tests which have survived are simply variations in method of arriving at the same result, and one is to be preferred to another merely for greater ease or quickness of performance. No attempt will be made to discuss all the tests for renal function, but rather those few which seem to cover the different phases of nephritis as it is viewed at present. No single test is of paramount value, but when the knowledge obtained from repeated tests is considered with the results obtained by the more usual methods of examination, we have a much more rational basis for making a prognosis and for

directing treatment intelligently. Frequently we are able to detect a serious condition which has not been previously suspected. From the standpoint of diagnosis in acute and in advanced chronic cases these tests have little to offer, the usual methods of clinical and physical examination being sufficient; but as an aid in prognosis and in rational handling of the case, particularly with reference to diet, they are of great value, especially when their repetition, after a period of weeks or months, gives two sets of figures for comparison, from which not only the amount of kidney damage but also the rate of progress of the lesion may be estimated. With the perfection of these tests we may expect eventually to place the dietary treatment of nephritis on as rational a basis as is the present dietary treatment of diabetes.

In general the tests fall into two groups, those which attempt to determine renal function by measurement of the excretion of chemical substances which have been introduced for that purpose, and those which are designed to measure the retention or excretion of food substances and the waste products of metabolism.

Nephritis in children differs widely in many respects from nephritis in adults, in whom the cases fall into one of two main groups, the second being by far the larger. The first group is composed of renal infections, either acute or chronic, which are secondary to an infectious process elsewhere in the body. The second group is of the chronic type associated with degenerative changes in the vascular system. This second type is so rare in childhood that it need not be considered as a practical problem for our purposes, and we may assume that our cases will all correspond to the form in which the nephritis is secondary to an infective focus, whether they be at present acute or become chronic. In comparison with the amount of research which has been done on some of the other problems of pediatrics, the investigation of nephritis has been neglected, and we are forced to draw to an undesirable extent on information secured from a study of adult conditions, and, unfortunately, largely on conditions obtaining in the form of nephritis which is uncommon in childhood. We are surely not justified in assuming without definitely positive evidence that functional tests may be interpreted alike in children and in adults. In so far as comparisons have been made, however, it seems evident that there is no essential difference in their significance,[1] although in general the secretory capacity of the child's kidney seems to be somewhat greater than that of the adult.[2]

It has been repeatedly questioned whether adults ever entirely recover from an acute nephritis, and in any case the prognosis for complete recovery of function is doubtful. In children, however, we may predict a much happier outcome. Ernberg[3] examined 40 adults who had had an acute nephritis before the age of 15 years and found normal urines in all. Of 16 other cases in whom nephritis had occurred between the ages of 15 and 30 years, all except four were normal. Two of these showed evidence of a recent reinfection, and the other two, whose original infection had been subacute, showed albu-

minuria. He concludes: "If these figures give us a true picture we certainly have been unduly pessimistic about the prognosis of acute nephritis in childhood." Hutinel[4] also believes that the nephritis of childhood almost always tend towards recovery, but Apert[5] suggests that the ease with which compensatory hypertrophy and repair take place in the kidney of the infant and child may mask a slight but permanent degree of damage and leave an apparently normal kidney which is susceptible to reinfection later in life.

Nephritis is not the only condition in which we find a lowered renal function, nor is an extremely poor function always incompatible with the expectation of a considerable duration of life. In severe anemia the output of phenolsulphonphthalein may be very low and there may be marked fixation of the specific gravity of the urine.[6] Similarly, there may be a low phthalein excretion, without retention of blood urea nitrogen, in chronic passive congestion,[7] and the same is true of orthostatic albuminuria,[8] presumably from anemia of the kidney resulting from constriction of the renal vessels. According to most investigators, during and immediately following the acute infectious diseases the renal function is in no way impaired in cases which show no clinical evidence of nephritis.[9] Although a persistently low function is of grave prognostic import it does not always mean immediate incapacity or death. O'Hare[10] reports the case of a girl who had an acute nephritis at the age of nine years, following scarlet fever. She was seen at the age of 23 years with a chronic nephritis and carefully followed until her death, three years later. During that time she led a carefully regulated life, but at no time did her phthalein excretion exceed 18 per cent., and during the last year no excretion could be measured. Her blood urea nitrogen, meanwhile, remained over 50 mg. per 100 c.c. of blood. Similar results are recorded in the case of a second patient whose manner of living was not at all regulated, and who for five years had a phthalein excretion of below 14 per cent., his blood urea nitrogen being constantly four or five times the average normal.

THE PHENOLSULPHONEPHTHALEIN TEST

This test, as described by Rowntree and Geraghty,[11] has been found, through several years of application, to be a simple and practicable procedure, easy to perform and requiring little in the way of special apparatus. It is carried out as follows:

Six milligrams of the dye phenolsulphonephthalein is injected intramuscularly. If possible the patient is given a moderate amount of fluid (200 c.c. for an adult) to promote diuresis, and a like amount of fluid is given at the end of one hour. At the end of two hours the urine is collected, made alkaline with sodium hydroxide to bring out the color, and diluted to 1000 c.c. This solution is then compared to a standard solution to determine the intensity of color, the result being

expressed in the percentage of phthalein excreted in two hours. In the case of infants or of very young children, who cannot be made to hold the urine or to void at will, it is usually necessary to introduce a catheter which is held in place throughout the test by strips of adhesive.

The normal excretion for adults is somewhat below that for children, and averages between 50 and 80 per cent., the former figure being the low normal limit. Figures for the normal phthalein excretion of infants and children vary somewhat with different observers, but all agree that they are higher than for adults. Figures from various investigators average about 75 per cent.,[12] which we may take for the normal. In acute nephritis, however, the relations are reversed, the phthalein excretion being lower in children than in adults. Atchley[13] asserts that an excretion of over 20 per cent. is not cause for grave concern, while one below that figure gives a poor prognosis. This statement is not to be accepted without limitations, for not infrequently a high phthalein excretion occurs in either an acute or chronic nephritis which, from the course of the disease and from other functional tests, is known to be severe. We may consider that in general the measurement of phthalein excretion in acute nephritis in children is of value in determining the severity of the condition only when it is much below normal. It should be remembered that in cases with edema, whether due to nephritis or to cardiac disease, a low excretion will improve as the edema disappears. In general it seems that the percentage of phthalein excretion is roughly proportionate to the amount of renal damage. In chronic nephritis the excretion is likely to be higher than in acute nephritis and correspondingly higher than in the chronic nephritis of adults, in whom the condition is usually more severe. Excretion in chronic nephritis, therefore, is of significance when it is persistently lowered even a relatively small amount.

ESTIMATION OF NON-PROTEID AND BLOOD UREA NITROGEN

When the kidneys have been sufficiently damaged to interfere to any great extent with their power of excretion, we find that there is a retention within the body of the normal waste products of metabolism, made up of various elements in combination with nitrogen. This is designated as "non-proteid" nitrogen and includes that contained in the urea, creatinin, amino-acids, uric acid and ammonia which remain in the filtrate after the proteins of the blood have been removed by coagulation. A quantitative determination of the non-proteid nitrogen of the blood, therefore, gives indication whether the above substances are being excreted normally, or whether they are accumulating in the body because of the kidney's decreased deficiency. The excretion of all of these substances is of importance, but the separate determination of the urea excretion has received more attention than has any of the others, and it is the one which, at present, we may consider of the greatest importance.

There is a considerable normal variation in the amount of non-proteid nitrogen in the blood, depending largely on the length of time which has elapsed since the previous meal. This variation is apparently greater in children than in adults, and differences as great as 34 mg. per 100 c.c.[14] have been found in samples taken just before the noon meal. In blood which is taken after a 12 hour fast or in the morning before breakfast the amount of non-proteid and urea nitrogen is relatively constant, and for this reason it is best to obtain samples of blood after a fasting period. Normally the amount of blood urea nitrogen is about one-half the amount of total non-proteid nitrogen, figures for adults and children corresponding closely. We may expect that the blood of a normal child who has been fasting will contain between 24 and 28 mg. of non-proteid nitrogen per 100 c.c. Leopold and Bernard,[1] in studying a series of 50 children without kidney disease, found that there was considerable variation in the amount of blood urea nitrogen. Their lowest figure was 8 mg., and their highest 21 mg., giving an average of 12 mg. per 100 c.c. for the whole group. Only one case, a cardiac, was over 15 mg. According to the results obtained by Squier and Myers[15] and Kast and Wardwell,[16] it appears that a figure above 20 mg. is certainly abnormal, and in some cases this may be true of one above 15 mg. We may consider that our standard for blood urea nitrogen is below 15 to 20 mg. per 100 c.c. of blood.

On account of the better secreting capacity of the kidney and the relative mildness of the nephritis in children, nitrogen retention is much less common than in adults. When it does occur it is of considerable prognostic value and indicates that the disease is severe. Chapin and Myers[2] report recoveries in three cases of acute nephritis with a blood urea nitrogen of 50, 59 and 70 mg., respectively, and one in which retention was due to an injury causing supression of urine, where the nitrogen rose to 106 mg. Their figures indicate that there may also be a transient increase in the blood urea nitrogen to over 20 mg. in some of the severe, acute infections such as pneumonia and enteritis, but others have found no increase in these conditions. Although the above figures are somewhat higher than those reported by others, they are not quoted to oppose the opinion that in acute nephritis the severity of the disease may be roughly gauged by the amount of urea retention, and that any measurable retention in children indicates a serious condition. A nitrogen retention of any degree in chronic nephritis indicates permanent damage and warns of approaching uremia. However, uremia may supervene without a measurable nitrogen retention. This is usually in cases which are so edematous that the resulting hydremia has reduced the percentage of nitrogen in the blood by dilution.

Formerly blood nitrogen determinations were made by methods so difficult and complicated that special training and an elaborate laboratory equipment were necessary. Simpler methods,[17] which are practicable for use in a small laboratory by the average well-trained physician, have lately been devised.

THE TWO HOUR TEST

During every 24 hour period the kidney is called upon to vary the concentration of the urine in accordance with the intake of water, protein and salt to insure that the composition of the body fluids be maintained at a constant level. This concentration varies inversely with the fluid intake, and directly with the salt and protein intake. In other words, the specific gravity of the urine may be raised by diminishing the amount of water or by increasing the protein and salt intake, and it may be lowered by drinking a large amount of water. Measurement of the kidney's ability in this respect has been made the basis of a test of renal function, commonly called the "two hour" test, originally proposed by Hedinger and Schlayer[18] in 1914, and used extensively in this country by Mosenthal[19] and O'Hare.[20]

If samples of the total amount of urine passed in 24 hours were taken on several successive days it would be found that the specific gravity changed but little from day to day, for the total protein, salt and water intake for any number of 24 hour periods is very likely to be relatively constant when the patient's appetite is the guide to his diet. But if the urine is collected over shorter intervals varying concentrations will be found, corresponding to the time and composition of the meals. The principle of this test, then, is to test small amounts of urine at relatively frequent intervals during the 24 hours. An average diet is usually sufficiently varied to meet the requirements of the test, for the morning meal is light and contains a considerable amount of fluid, at noon there is more salt with vegetables and meat containing purine bases which act as diuretics, and at night the meal consists mostly of carbohydrates and fluid. The prime requisite is that one meal shall contain a relatively large amount of protein and salt. A normal kidney will necessarily have to produce a much more concentrated urine after a noon meal, as described above, than after either breakfast or supper. A rather wide variation in diet is compatible with good results, for if the kidney is diseased the curve of excretion will always tend to show a departure from the normal by being flattened. In performing the two hour test the urine is collected every two hours from 7 a.m. to 7 p.m., and the night urine passed from 7 p.m. to 7 a.m. as a separate specimen, the amount and specific gravity of each specimen being recorded. Elaborations of this test, as described by Mosenthal, O'Hare and others, include comparative quantitative determinations of the protein, salt and water intake and output; but for most practical purposes of clinical work sufficient information may be obtained from a determination of the specific gravity, and from a comparison of the total day and night amounts of urine.

In both adults and children the fluid output is about two-thirds of the fluid intake, the remainder being excreted through the lungs and the skin. A normal adult on a fluid intake of about 1800 c.c., distributed through the 12 hours from 7 a.m. to 7 p.m., will secrete 600 c.c. or less of urine during the night, or about one-third of the total intake.

Secretion of a greater amount than this indicates that there is a retention of solids which the kidneys have not excreted during the day because of their inability to concentrate the urine beyond a fixed point. During the night when no protein or salt intake occurs, they are able to get rid of this excess only by excreting an abnormally large amount of urine which they have concentrated to the extent of their ability. This is frequently the case when there is salt retention, the excess of salt being accompanied by an excess of water which has been retained for the purpose of holding the salt in solution. Such a condition, of course, amounts to an edema, but is often present to such a small extent that, although it is measurable by the two hour test, it cannot be demonstrated clinically. We may consider that when the amount of night urine much exceeds one-third of the total 24 hour amount, there is evidence of retention of one or more of the solids. Faulty excretion may involve either water, total solids, nitrogen, salts, or all of these substances, but the nitrogen excretion is usually fairly normal after disturbance in the excretion of water, total solids and salt has taken place.[21]

The following table from Hill[2] illustrates normal and abnormal variations in the specific gravity of the various specimens:

Normal response (normal child 11 years old)		Abnormal response (severe chronic nephritis, 5½ years)	
Time	Specific gravity	Time	Specific gravity
6–8	1.018	6–8	1.017
8–10	1.010	8–10	1.018
10–12	1.015	10–12	1.019
12–2	1.021	12–2	1.018
2–4	1.017	2–4	1.018
4–6	1.021	4–6	1.019
6–6	1.023	6–6	1.019

In the 15 normal children studied by him there was a difference of eight or more points between the highest and lowest specific gravity of the two hour specimens. In every normal case, except one, the gravity of the urine was over 1020, but the amount of night urine varied too much to determine a normal standard. In nearly all of his cases of nephritis there was a fixation of gravity, and several showed abnormal two hour tests although the phthalein excretion was normal.

Figures obtained by this test must be interpreted with caution, for so many factors are concerned in the variation of the gravity of the urine that a rather nice distinction is often necessary to decide which one or ones is responsible in a given case.

It is evident that no single test described above will yield complete information about the condition of the kidneys. The tests represent variations in method of determining the same thing, whether or not the kidneys are excreting the proper amount of fluid and solids to miantain the concentration of the body fluids at the physiologic level. They vary in value as conditions vary in different cases, and not all are applicable to every case, although the phthalein test is probably the most useful for routine work. Considering the relative mildness of nephritis in children, however, it seems likely that the two hour test, which has proved to be one of the most delicate tests in adult nephritis, will be found especially adapted for use with children. It should be of especial value to the practitioner, since no apparatus other than a measuring glass and a urinometer is required.

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CHAPTER XCVII

ENURESIS

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Much has been written but relatively little is known of this condition which distresses mothers, shames children and frequently baffles physicians. Enuresis should be defined as the persistence from early infancy or the development during childhood of unintentional and usually unconscious nocturnal or diurnal emptying of the bladder in the absence of demonstrable organic nervous or genito-urinary lesions. Often, however, the condition is referred to, solely as "bed wetting" although more than half of the patients (Table 1) are also afflicted with

Table 1.—The Case Distribution of Diurnal and Nocturnal Incontinence

Symptoms	Number of patients	Case distribution per cent.†	Case distribution reported by other authors		
			Zappert[1]	Holt[2]	Still[3]
Both diurnal and nocturnal incontinence	378(89)*	64.0	56.0	55.5	44.0
Nocturnal incontinence alone	204(48)	34.5	44.0	39.6	52.0
Diurnal incontinence alone	9(2)	1.5	0.0	4.9	4.0
Total	591(139)‡	100.0	100.0	100.0	100.0

* A total of 591 enuretic patients attended the Harriet Lane Home dispensary from 1912 to 1922 inclusive. The case histories of 200 of these patients were analyzed and from the data obtained, the figures for the total of 591 patients were calculated. The first figure in each group indicates the calculated total number of enuretic patients occurring in each group and the figure in brackets indicates the actual number of the 200 patients in each group.

† Case distribution refers to the percentage of enuretic patients in each group.

‡ A statement of the presence or absence of diurnal incontinence was omitted from 61 of the 200 case histories analyzed.

inability to contain their urine during the day. Most normal children acquire, or are taught the ability to control the act of urination by the age of two and one-half years, so that after this age, incontinence of urine may usually be diagnosed as enuresis.

In the majority of instances, enuresis dates from earliest infancy (Table 2). These children have never learned to control their

TABLE 2.—AGES AT WHICH ENURESIS DEVELOPED AND THE CONDITIONS TO WHICH THE DEVELOPMENT OF ENURESIS MIGHT POSSIBLY BE ATTRIBUTED

Age at which enuresis developed	Number of patients	Case distribution, per cent.†	Conditions to which the development of enuresis might possibly be attributed					
			Neuropathic constitution (neurosis) nervousness, per cent.	Mental retardation per cent.	Intestinal parasites (oxyuris, taenia, ascaris) per cent.	Phimosis, per cent.	Miscellaneous conditions, § per cent.	No obvious cause, per cent.
From earliest infancy "congenital"	510(173)*	86.5	18.5(32)‡	3.5(6)	2.3(4)	2.3(4)	4.4(7)	69.0(120)
Two to ten years "acquired"	81(27)	13.5	18.5(5)‡	0.0	3.7(1)	0.0	18.5(5)	59.3(16)
Total	591(200)*	100.0	18.5(37)	3.0(6)	2.5(5)	2.0(4)	6.0(12)	68.0(136)

* See the first footnote to Table 1.

† See the second footnote to Table 1.

‡ These percentages indicate the percentage of cases in each group ("congenital" and "acquired") in which these conditions may possibly have caused the development of enuresis.

§ Each of the following miscellaneous conditions was diagnosed as the cause of the development of enuresis in one case: Trauma to perineum, cervical rib, orthostatic albuminuria, scaphocephaly, congenital abnormality of the lumbo-sacral spine, inguinal hernia, epilepsy, Duchenne—Erb paralysis, syphilis, tonsillitis, circumcision, measles and pertussis.

bladders. Other patients, have had cleanly habits for several years and have then gradually or suddenly developed enuresis. It is interesting that the frequency of diurnal incontinence is the same in the two groups. In fact no difference can usually be discovered in the symptoms of these two classes of patients. Dysuria is uncommon, occurring in only 3 per cent. of each group. Usually phimosis or some similar cause is responsible for this symptom. Many patients have increased frequency of urination (pollakiuria), although some children who have pollakiuria do not have enuresis. The passage of abnormally large amounts of urine (polyuria) is but infrequently associated with enuresis. It is often stated that enuresis is worse during the winter months but this is probably infrequent as it was noted in only one of our patients. Another patient said the condition was worse during the summer. Fecal incontinence is uncommon among enuretic patients except in the mentally retarded.

The parents or attending physician will often attribute the development of enuresis to some underlying condition. Among the group who have "acquired" enuresis, it is possible that such conditions as tonsillitis, pertussis or circumcision, may have been contributing factors. It is also possible that in children who develop incontinence after the age of six years, especially those with frequency of urination, the excitement of going to school and the restriction of toilet facilities may precipitate enuresis. Chorea and rheumatic fever played no obvious rôle in any of our cases although Still[3] believes these diseases may be of etiologic importance. In the "congenital" group, mental retardation, as might be expected, is responsible for a few of the cases. Many mentally retarded children never learn to control their sphincters. The fact that the same percentage of patients in each group had neuropathic constitutions would seem to indicate that both "congenital" and "acquired" enuresis is much the same disease. Spina bifida may occasionally cause enuresis. Among a total of 591 enuretic patients many of whom were examined roentgenologically, there were four with spina bifida. Three of these had both urinary and fecal incontinence, and one had only urinary incontinence. One other child had spina bifida and fecal incontinence, but no enuresis. Approximately two thirds of the patients had no obvious underlying condition to which the development of enuresis could be attributed.

Enuresis is an exceedingly common disease. One child in every 56 attending the Harriet Lane Home dispensary was brought in because of this condition, (Table 3). White children are much more commonly affected than colored. It has been suggested that this racial difference is due to the fact that colored parents do not pay much attention to "bed wetting." However, among the poorer classes in Baltimore, colored children are usually better cared for than white children, so that the infrequency of enuresis among the former probably does not depend upon any failure of the parents to notice the condition. It is likely that the relative infrequency of neurotic and neuropathic condi-

tions among colored children is connected with this infrequency of enuresis. In both races the disease is somewhat more common among boys than girls.

Table 3.—The Relation of Sex and Color to Case Distribution and Case Incidence

Sex and color	Number of enuretic patients	Case distribution of enuretic patients,† per cent.†	Case incidence of enuresis in Harriet Lane Home dispensary per 100 patients‡
Male, white	295(100)*	50.0	2.33
Female, white	216(73)	36.5	1.88
Male, colored	44(15)	7.5	0.96
Female, colored	36(12)	6.0	0.88
White (both male and female)	510(173)	86.5	2.1
Colored, (both male and female)	81(27)	13.5	0.97
Male (both white and colored)	341(115)	57.5	1.97
Female, (both white and colored)	250(85)	42.5	1.61
Total	591(200)*	100.0	1.79

* See the first footnote to Table 1.

† See the second footnote to Table 1.

‡ The case incidence has been calculated on a basis of 591 enuretic patients among a total of 32,892 patients (all diseases) who attended the Harriet Lane Home dispensary from 1912 to 1922 inclusive.

Enuresis is undoubtedly much more prevalent than is indicated by Table 3 for there are probably many additional children in whom the condition has disappeared before the parents deem it of sufficient importance to seek medical advice. The average age at which our patients were brought to the dispensary complaining of incontinence was seven years.

Two or more cases of enuresis are sometimes found in one family. This may be due to the fact that all of the children are neuropathic or because a younger child imitates an older enuretic brother or sister. Enuresis is occasionally hereditary. The parents of one of our patients reported that the child's grandfather, mother and uncle had had enuresis from the age of two and a half years to puberty. In boarding schools, as a result of imitation, enuresis has been known to become prevalent after the admission of an enuretic child.

Enuresis is probably equally as common in the children of the wealthy and poor classes. During the Great War, however, the enuresis that was reported among troops was much more prevalent among enlisted men than among officers. This difference may have

been due to the greater hardships undergone by the former. Many of the soldiers who developed enuresis were neuropathic and had suffered from the condition during childhood.[1,4] This war enuresis was frequently associated with "colds" and was often preceded by exposure to wet and cold.

Zappert[1] to whom I am endebted for many details has recently written a most comprehensive article on enuresis, which should be consulted for a complete analysis of the subject. He has compiled most of the descriptions and methods of treatment of enuresis and all of the theories in regard to its etiology from the time of Hippocrates.

Theories in Regard to the Etiology of Enuresis.—Anatomic Theories.—Dittel[5] in 1872 thought that the condition was due to a lack of development of the prostate and of the internal sphincter of the bladder. It is quite true that some patients have very small undeveloped prostates but the fact that enuresis occurs nearly as frequently in girls as in boys suggests that lack of development of the prostate has no relation to the condition. Some clinicians have maintained that there were changes in the normal functions of the sphincter and detrusor muscles of the bladder. Hyperexcitability of the sphincters and abnormally powerful detrusor muscles have been described. It is also stated that a definite weakness of the sphincters is present and that although by voluntary effort the patients prevented incontinence during the day, yet when the muscles were relaxed at night, enuresis developed. Van Tienhoven[6] believed that, because raising the foot of the bed cured "bed wetting" in some children, the cause of enuresis was the escape of a drop of urine through a weak sphincter into the prostatic portion of the urethra and the consequent excitation of urination.

Guyon[7] in 1897 suggested that the lowered tonus of the sphincters might be the cause of enuresis because in passing sounds he encountered subnormal resistance. Kapsammer[8] interpreted the beneficial results he obtained by epidural injections of normal saline, as due to stimulation of the spinal cord and a consequent increase in the tonus of the bladder muscles. Testing the pressure of the bladder with manometers has demonstrated that hypotonus exists in some patients but not in others. Zappert[1] reported that when water was injected into the bladders of normal and enuretic soldiers a series of bladder contractions occurred. The normal individuals felt these contractions and by voluntary effort controlled their sphincters and thus retained the fluid but the enuretic patients were unconscious of any contractions and therefore failed to make an effort to hold the water. It is possible that there is some sensory abnormality of the bladder, because fluid heated to 48°C. may be injected into the bladders of enuretic patients without producing discomfort.[1] Still[3] suggests that enuresis may sometimes be due to disorders of the afferent nervous paths for many patients do not know that they have urinated, until they later discover that their beds or clothing are wet.

The connection of adenoids and mouth breathing with enuresis has been frequently emphasized. It has been assumed that because of the difficulty in breathing there is an increase in the carbonic acid of the blood and that this causes enuresis. This theory is unsound both on logical and chemical grounds. Enuresis may be temporarily improved by the removal of the tonsils and adenoids but the condition often recurs a few weeks or months later even though the tonsils and adenoids have been completely and permanently excised. It is probable that the temporary benefit from tonsillectomy is psychic in origin for many other operations have the same effect.

Developmental defects in the central nervous system and infectious or inflammatory changes in peripheral nerves have been advanced as causes of enuresis.[9] Fuchs[10] claimed that enuresis was due to a lack of development of the spinal cord. He believed that many enuretic patients have spina bifida even though in some instances it cannot be demonstrated roentgenologically. However, one of our five patients with spina bifida had no urinary incontinence though he could not control his feces. Fuchs[10] also reported that other developmental defects such as syndactylism, flat foot, pilonidal sinuses, disorders of reflexes and of the sensibility of the toes and ankles were associated with enuretic symptoms. However these and many other developmental defects are frequently found in individuals who do not have enuresis.

Abnormal Urine.—It has been said that excessively acid or alkaline urine or cystitis or pyelitis might cause enuresis. However, many of our patients have improved while taking large doses of sodium bicarbonate or potassium citrate so that it is improbable that the presence of very alkaline urine is a predisposing factor. Frequency of urination is of course a frequent symptom of cystitis and pyelitis but these diseases are quite different from enuresis. Occasionally the pollakiuria and polyuria of diabetes may give rise to enuretic symptoms so that the urine should always be examined for sugar.

Faulty Diet.—Because enuresis was more frequent in Germany during the war it has been suggested that faulty diet may be the cause of the disease.[1] However an analysis of many cases demonstrates that the diets of enuretic patients are usually the same as those of normal children.

Psychiatric Theories.—Janet[11] in 1890 stressed the importance of dreams of urination and other psychiatric states, as inciting factors in this disease. However Zappert[1] called attention to the fact that these dreams usually develop years after enuresis has been established and that furthermore many enuretic children have no such dreams. Some psychiatrists believe that enuresis is a juvenile equivalent of masturbation or of nocturnal pollution.[12] The long duration of the disease and the absence of hysterical features are arguments against the idea which is occasionally advanced that enuresis is a manifestation of hysteria. Many enuretic patients are exceedingly placid individuals.[1]

Laziness and lack of care are also believed to be at the basis of enuresis, but the majority of our patients did not appear to be lazy and many of them were really seriously concerned about their condition.

Profound Sleep Theory.—It is frequently noted that enuretic patients sleep very soundly. Many therefore believe that the slumber is so deep as to be below the threshold for the normal rousing reflex for evacuation of the bladder.[13] On the other hand, many children who are exceedingly difficult to waken never have enuresis. Furthermore, normal children do not have to empty their bladders at night even though they may contain a large quantity of urine.[1]

Neuropathic Theories.—Guinon[14] in 1889 was one of the first to emphasize the neurotic nature of enuresis. Pfister[15] believed that enuresis was evidence of an hereditary neuropathy. About one-fifth of our patients were distinctly neurotic, but the remainder, as far as could be ascertained by ordinary observation, were of stable mentality.

These theories explain but a very small percentage of the cases. In only one-third of our patients was there any condition to which the development of enuresis could possibly be attributed (Table 2) and even in these children this connection was very problematic. The most important etiologic factor appears to be the neuropathic constitution that was present in 18.5 per cent. of our patients. It is possible that in many instances enuresis is comparable to habit spasms, stuttering, or tics. The lack of early intensive training in regular habits of urination is certainly responsible for some cases, in much the same way as faulty home training leads to the formation of slovenly table manners which later are difficult to eradicate.

Treatment.—The types of therapy that have been recommended in enuresis are legion. The majority of patients can be cured or improved if practically any treatment is persisted in. The percentage of cured and improved patients indicated in Table 4 is perhaps too high for it is probable that many of the 125 patients whose course could not be followed were individuals who, either through lack of coöperation or otherwise, failed to improve. At least one-seventh of the patients were unaffected by treatment. Fortunately, most of the latter acquire the ability to control urination by the age of puberty or even later in adult life. A few individuals suffer from recurrences of enuresis throughout their lives.

Every patient should be thoroughly examined for the presence of spina bifida, infantile bladder, pyelitis, diabetes, cystitis, renal, ureteral or vesical calculus, phimosis, abnormal clitoris and other conditions which can cause frequency of urination, and incontinence. As a general rule with the exception of spina bifida occulta, the presence of other symptoms, in addition to incontinence, suggests the existence of the above conditions. These patients are usually promptly cured as soon as the underlying cause has been appropriately treated. In some cases of enuresis due to spina bifida occulta, the removal of a pad of

TABLE 4.—COMPARISON OF VARIOUS TYPES OF TREATMENT IN 75 PATIENTS WHOSE COURSE WAS FOLLOWED FOR VARYING PERIODS UP TO FOUR YEARS (THE COURSE OF THE REMAINING 125 PATIENTS OF THE SERIES COULD NOT BE FOLLOWED

Type of treatment	Number of patients treated	Cured		Improved		Unimproved	
		Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage
Fluid restriction and awaking (alone)	25	9	36.0	15	60.0 (96.0)*	1	4.0
Fluid restriction and drugs†	39	6	15.4	27	69.2 (84.6)	6	15.4
Drugs† (alone)	11	1	9.1	6	54.5 (63.6)	4	36.4
Totals	75	16	21.3	48	64.0 (85.3)	11	14.7

* The figures in brackets indicate the combined percentages of cured and improved patients.

† The following drugs were used either alone or combined: Sodium bicarbonate or potassium citrate in sufficient doses to keep the urine alkaline, tincture of belladonna or atropin sulphate in doses just insufficient to produce flushing of the face, benzyl benzoate in small doses and M. G. A. (mistura gentiani alkalinis) in small doses (*i.e.*, for psychic effect).

fibro-cartilaginous tissue which may be compressing the dura and cauda equina may immediately and permanently cure the incontinence.[16]

There are two essential features in the treatment of uncomplicated enuresis; first, the limiting of the fluid intake after 4 p.m. and the emptying of the bladder on retiring and again at 11 or 12 p.m. and, second, the establishment of the patient's confidence in his ability to be cured, either through his faith in the instructions given by the physician or through his reliance on the drugs prescribed. Probably the main reason for the success of some physicians with this condition and the failure of others lies in the ability of the former to command the patient's coöperation in whatever treatment is advised. Without coöperation on the part of the patient and also of the parents, treatment is frequently useless.

The instructions usually given are that no fluid of any kind shall be taken after 4 p.m. If the child has been accustomed to milk or soup with his evening meal, these are transferred to his noon meal. The patient is sent to the toilet at 8 p.m. and kept there until urination occurs. In some instances a child will not empty his bladder until he has been at stool for a half hour or more. He is then put to bed and awakened at 11 or 12 p.m. and again kept in the toilet until he urinates. Frequently the child will fall asleep at stool without emptying his bladder so that he must be watched and roused. It will be found that some children wet the bed before 11 p.m. so that awakening at 9 or 10

p.m. may be necessary. Regular times of urination, five to six times during the day, should be insisted upon. If this treatment is unsuccessful after two weeks, an additional awakening and urination at 2 or 3 a.m. are advised. With a few patients whose parents will not coöperate, the treatment just outlined must be carried out in the hospital. Practically all patients are cured by hospital care but in order that recurrences may not take place as soon as the patient returns to his home, hospital treatment must be continued at least three weeks. Usually by that time the patient has acquired the habit of emptying his bladder before retiring and of awakening spontaneously before midnight to urinate again. Enuretic patients must be followed, instructed and encouraged for at least one year before a permanent cure is established. Even then recurrences are frequent, especially in those children who have pollakiuria. Psychic depression, excessive exertion, excitement, digestive disturbances and illnesses are the usual precipitating factors in recurrences.

The second feature of treatment is purely suggestive[17] or psychic but just as essential as the instructions for fluid restriction and awakening. The physician should make every effort to gain the confidence of the child. Usually this is accomplished by friendly encouragement. Scolding, threats, terrifying, and punishment are useless. One of the most effectual systems is to arouse the child's play or game instinct by supplying him with a calendar so that he may paste a gold star over every date on which he has not wet the bed or his clothes. The child should return to the physician regularly every week or 10 days and receive some reward for good conduct.

The percentage of cured and improved patients is usually increased if the child can obtain one or two hours of rest or sleep during the afternoon.[13] This benefit may be due to a reduction in the depth of the child's sleep during the night or to a general improvement in the patient's nervous condition. Rest during the afternoon, however, is often impossible for children attending school. The prevention of excitement or strenuous play for a period of two hours before retiring often has a strikingly beneficial effect on enuresis.

The majority of children if properly encouraged will coöperate and be cured. However there are a certain number, often handicapped by uncoöperative parents, in whom drug therapy is usually necessary. The tincture of belladonna or a solution containing one-tenth of 1 per cent. of atropin sulphate,[18] in doses of five drops three times a day (for a child of six years) is frequently prescribed for antispasmodic effect. This dosage is then increased daily by one drop until the physiologic reaction of flushing of the face is obtained. The amount is then reduced 25 or 30 per cent. and administration continued for several days. These drugs must always be used cautiously for some children are very sensitive to them. In addition to belladonna and atropin, sodium bicarbonate, M.G.A. (mistura gentiani alkalinis), pituitary extract, luminal, adrenalin, or any other drug prescribed with

sufficient assurance will, in about half the cases (Table 4), improve the patient's condition. Zappert[1] has compiled a list of over 30 drugs that have been advocated for the treatment of enuresis. Since practically any drug seems to accomplish the same result it is probable that the explanation of their benefit is psychological rather than pharmacological. If drugs are combined with fluid restriction and awakening, the percentage of cures will be increased over that obtained by drugs alone (Table 4). Probably the reason that the group treated by fluid restriction and awakening (without the prescription of drugs) (Table 4) contains the highest percentage of cured and improved patients is because this group contained a greater proportion of coöperative children who did not require placebos in the form of drugs.

Unfortunately, even in the presence of excellent coöperation, improvement may sometimes fail to occur. For these refractory patients, various measures have been recommended. As a general rule, however, they have not been as successful as fluid restriction, awakening and suggestion. Corrigan[19] advised sealing the urethral opening at night with collodion. Others have tried pressure bandages over the meatus as well as pressure on the urethra applied through the rectum. These procedures produce more discomfort than improvement. Raising the foot of the bed at night has reduced the incontinence of some patients. The administration of hot or cold sitz baths or of shower baths to the shoulders before retiring has occasionally been of benefit. Massage of the neck of the bladder through the rectum, electrical stimulation of the bladder sphincter by placing one electrode over the pubis and the other on the perineum or in the rectum, and even exposure of the lower abdomen to Roentgen-rays will sometimes improve enuresis probably because of their psychological effect on the patient.

Special diets[17] with very light suppers and the drinking of alkaline table waters have been advised. Coffee and tea are usually prohibited because of the production of diuresis and nervousness. However, some clinicians prescribe tea and coffee before retiring so that the child will sleep less soundly.

The passage of sounds to dilate the urethra and the injection at frequent intervals of large amounts of fluid into the bladder to accustom that organ to the presence of large amounts of urine are said to be beneficial. The danger of producing cystitis, however, more than over-balances any improvement in enuresis that may be obtained. Surgical operations on the adenoids, clitoris and other organs frequently arrest, though usually temporarily, the course of enuresis. This effect is probably of psychic origin. In some instances the injection of normal saline into the spinal canal has cured enuresis. This procedure however, is too drastic to be of much general use. Hypnotism and Freudian psycho-analytical methods have occasionally cured enuresis when all other measures have failed.

For patients who apparently can not be cured and especially for permanently mentally retarded children whose prognosis is often hopeless, a mattress with a central opening similar to those used for metabolism studies has been advocated. Its only merit of course, is the prevention of damage to the mattress.

Prophylaxis.—Inasmuch as the successful treatment of enuresis requires such a tremendous amount of care on the part of both the physician and the parents it would seem logical to concentrate more attention than is usually paid to it, on the proper training of infants in regular habits of urination. As a general rule, commencing at the age of six months or as soon as an infant is able to sit up, the placing of the child on a chamber or modified toilet immediately before each nursing will, within a few months, establish regular habits of urination and defecation. These habits, in practically all instances, may be made permanent by providing the child with regular opportunities for the emptying of the bladder and rectum. The frequency of normal urination is very variable and depends upon many factors such as the amounts of fluid taken, exercise, perspiration and habit. Table 5 indicates the average daily number of urinations recorded by Camerer in a series of normal infants and children.

TABLE 5.—AVERAGE DAILY NUMBER OF URINATIONS OF NORMAL CHILDREN (CAMERER)

Age of child	Average daily number of urinations
5 months	13 to 16
2 years	6.9
3¼ years	4.8
5¼ years	5.0
9 years	4.4
11 years	4.0

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CHAPTER XCVIII

NEPHRITIS

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Definition.—Nephritis may be considered as a diffuse, progressive, degenerative or proliferative lesion involving renal parenchyma or interstitial tissue or both. Abscess and infarct are not included.

The conditions which constitute nephritis manifest themselves by a variety of signs. The urinary findings alone do not always suffice to make a diagnosis. Albumen and casts are often considered as pathognomonic features. However, they may appear in the urine from so slight a cause as a mild congestion of the kidney, and they may rapidly disappear, leaving no trace of permanent injury. If the abnormal urinary findings are transitory it may be surmised that only the early phase of the inflammatory process, namely, congestion, has developed. If casts and albumen persist, other clinical manifestations will confirm the diagnosis.

In certain types of chronic nephritis clinical evidence of disease may be absent although the pathologic changes in the organs themselves may be extreme. Kidney function tests and chemical examination of the blood and urine are important diagnostic factors. Other data, such as blood pressure and hemoglobin content, are of value in the diagnosis of nephritis.

Classification.—The purpose of any classification should be to present the features of disease in a complete and comprehensive manner. It should lead the way to better understanding of disease and to improved medical practice. Classifications of nephritis are based on etiology, pathologic anatomy, renal function and clinical manifestations. It is dufficult to reconcile specific renal pathologic anatomy with etiology or clinical findings.

An etiologic classification includes primary and secondary factors. The primary factors are infectious processes and toxic substances, such as mercuric chlorid, Fowler's solution, tar, iodin and phenol. Secondary types are those following exanthemata, gastro-intestinal disturbances, eczema, impetigo, pneumonia, tonsillitis and other general infections. Arteriosclerotic types which occur in adults are extremely rare in children.

The old pathologic classification of glomerular, parenchymatous and interstitial nephritis has been largely abandoned. According to Göppert and Langstein, the nephritides include (1) acute nephrosis,

(2) glomerulonephritis, and (3) chronic nephritis. Nephrosis consists of mild degeneration of the tubules with marked retention of chlorids and water, slight nitrogen retention, and no hypertension. Glomerulonephritis follows scarlet fever and throat infections. It is characterized by a destruction of the glomeruli, occasional hypertension, and occasionally hematuria. Salt and nitrogen are excreted with difficulty, and uremia may follow. They describe four types of chronic nephritis. Two are so rare that they may be simply mentioned, chronic interstitial and chronic nephritis with infantilism. The two more common types of chronic nephritis are the moderate and severe chronic parenchymatous nephritis. These do not differ from the adult forms. The mild or benign type of chronic parenchymatous nephritis is peculiar to early life and ends in recovery unless exacerbations occur transforming it into the severe type. As a rule the chronic form, irrespective of type, is based on an acute attack which is succeeded by a subacute stage persisting about a year.

DeBuys divided nephritis into the functional and organic types. He defines the former as an irritation of the kidneys discovered in a routine examination in high fevers, acute gastro-intestinal disturbances and acute infections. The irritation is caused by elimination of toxins, and the urine is normal except for hyaline casts. The urine is concentrated and diminished at the onset when the fluid intake is diminished. He believes that the kidneys are congested. The organic type is divided into acute and chronic and primary and secondary. This includes acute diffuse nephritis, glomerulonephritis, the parenchymatous form with extreme degeneration of the tubular epithelium, hemorrhagic form with hemorrhages into the tubules, glomeruli and interstitium, exudative form with leukocytes, serum and red cells in the glomeruli and tubules with variable changes in the parenchymal and interstitial tissues, and a productive form with early and severe changes in the interstitial tissue.

From the functional standpoint, Foster differentiates between nephritis with defective water and salt elimination and that with defective nitrogen elimination.

The classification of Volhard and Fahr* makes an attempt to divide the diseases according to pathogenesis. The clinical descriptions are

*(*A*) Degenerative diseases: Nephritis of real or known etiology with and without amyloid degeneration of the vessels.
1. Acute course.
2. Chronic course.
3. Final period, nephromiosis (renal atrophy) without rise of blood pressure.
(*a*) Necrotic nephritides.

(*B*) Inflammatory diseases: Nephritides.
1. Localized nephritides without rise of blood pressure.
(*a*) Localized glomerulonephritis.
i. Acute period.
ii. Chronic period.

not altogether adequate to explain the nephritis of infancy and childhood.

Larkin and Levy have modified Volhard and Fahr's classification to consist of acute and chronic glomerulitis, interstitial nephritis, and tubular nephritis or nephrosis, the last two of which are secondary to arteriosclerosis.

Acute glomerulitis is a true inflammatory reaction in the glomeruli with exudation and swelling of the tuft epithelium and increase in cells in and upon the tuft. This proceeds to repair and is seldom seen post-mortem. There is no increase in nitrogen except in the extreme oliguria after scarlet fever or anesthesia. Convulsions may occur at the onset but are independent of true uremia, and recovery usually occurs. There is no marked increase in blood nitrogen in this type. This fact is used as a differentiation from chronic glomerulitis in which the convulsions are usually uremic manifestations and the prognosis is not so good.

Chronic glomerulitis gives the highest blood nitrogen figures. Increase in blood nitrogen during the course of the disease is a bad prognostic sign. These patients succumb within a few years.

The arteriosclerotic type is primarily vascular, and the glomeruli and parenchyma are secondarily involved. There are various grades of atrophy and hyalinization of the glomeruli. Interstitial changes are moderate or marked, and the end result is a primarily contracted kidney. There is no nitrogen retention in the course of the disease. This type rarely occurs in childhood.

Nephrosis affects the tubules. There is characteristic fatty degeneration of the tubular epithelium. The blood nitrogen is within the normal limits. These lesions usually repair. Most cases of parenchymatous nephritis belong in this class. Edema may be marked.

From the practical pediatric standpoint Hill offers a classification in use at the Babies' Hospital in Boston. He recognizes five types: (1) Acute hemorrhagic, (2) acute exudative, (3) subacute, (4) chronic, mild or severe, and (5) chronic with infantilism. This classification is based on clinical findings.*

(*b*) Septic interstitial localized nephritis.
(*c*) Embolic localized nephritis.

2. Diffuse glomerulonephritides invariably with rise of blood pressure.
(*a*) Acute period.
(*b*) Chronic period without kidney insufficiency.
(*c*) Final period with kidney insufficiency.

All three periods may run their course (*a*) without nephritic complications, or (*b*) with nephritic complications, that is, with severe diffuse degeneration of the Epithelium (mixed form).

(*C*) Arteriosclerotic disorders: Sclerosis.

*Acute hemorrhagic nephritis yields a red urine with a moderate amount of albumen and a sediment chiefly composed of red cells, a moderate number of round epithelial cells and a few or no casts. Leukocytes may replace the red cells. The

ACUTE DIFFUSE NEPHRITIS

This includes those forms of nephritis which run an acute course with recovery, those which prove fatal during the acute stage, and those which pass from the acute to the chronic stage, depending on the extent of the initial injury to the tissues or the prolonged or repeated action of the etiologic agent.

Etiology.—**(A) General.**—There are at least three well-defined factors in the production of this type of nephritis:

1. Bacteria acting directly on the kidney tissue.
2. Bacteria acting through their products (toxins) either produced in the kidneys or carried there by the blood stream.
3. Toxic products, either bacterial or chemical, absorbed through the skin or mucous membranes and carried to the kidneys in the blood stream.
   - (*a*) Poisons (accidental) and drugs (Fowler's solution).
   - (*b*) Toxic products.
     1. Formed and absorbed in the intestinal tract, or
     2. Ingested as foods and acting as poisons when absorbed (foreign proteins).

(B) Specific.—In early infancy acute nephritis is usually caused by (1) the gastro-intestinal disturbances, particularly the alimentary

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amount of urine is little diminished, and there is no edema. The blood pressure is not elevated, and the heart is not enlarged. The child is not very ill and recovers fairly quickly.

Acute exudative nephritis gives a diminished amount of urine in the acute stage with many casts and epithelial cells and a moderate to large amount of albumen. Red cells are not so numerous as in the first type. The blood pressure is moderately elevated, and there is some enlargement of the heart. There is an inability to excrete salt, increased non-protein nitrogen in the blood, and more or less interference with phthalein excretion. The child is quite ill, and a small proportion die of uremia. Otherwise they are likely to recover completely without developing subacute or chronic nephritis.

Subacute nephritis usually develops from the first but may be insidious in its origin. It is often difficult to draw the line between these forms. Morse states that persistence of red cells and casts after three months without marked clinical signs justifies placing the case in the category of subacute nephritis. The urine contains little albumen and is not diminished in amount. The sediment contains few red cells, epithelial cells and casts, and the numbers vary from day to day. The blood pressure is not elevated, and the heart is not enlarged. There is little or no impaired function. The child looks and feels well. Almost all recover although it may take two or three years for the urine to clear. Occasionally these cases become chronic.

Chronic nephritis is relatively uncommon and follows the acute forms. The urine may be normal or greatly diminished. There may be much or little albumen. There are casts and cells of all kinds, but there is no blood unless there is an exacerbation. The blood pressure varies, but is usually increased although never to the degree found in chronic interstitial nephritis. The heart varies with the blood pressure. Function is impaired. The child looks and feels well in the mild form, but in the severe looks like the picture in chronic diffuse nephritis. Death may be long delayed.

Chronic nephritis with infantilism is rare.

intoxication of Finkelstein, although a simple dyspepsia may be attended with albuminuria; (2) infections such as pneumonia, meningitis and erysipelas; (3) diffuse skin eruptions of the exanthemata as well as eczema; (4) toxic substances particularly used as local applications, such as betanaphthol, phenol, tar, and other substances; (5) congenital syphilis; (6) congenital defects of the uriniferous structures.

In older children the most common causes are the acute infectious diseases, including tonsillitis, scarlet fever, diphtheria, rheumatic fever, otitis media, pneumonia, empyema, influenza, meningitis, typhoid fever, measles, chicken pox, small pox, erysipelas, whooping cough and mumps. Diffuse skin lesions play a large part, such as impetigo and eczema. It is believed that in some instances the sudden deaths which occur in certain cases of eczema are due to kidney disease. Hill and Morse attribute far more importance to tonsillitis than scarlet fever as a cause of acute nephritis. In 61 patients ill with nephritis, in one series, tonsillitis was the cause in 14. In order to determine the comparative frequency of acute nephritis in tonsillitis and scarlatina, statistical records of these diseases should be more carefully analyzed, based on accurate clinical observations.

Concerning the bacteriology, Miller states the etiology of acute nephritis is most often a streptococcus infection from the upper respiratory tract especially the tonsils and sinuses. Nephritis due to peridental infection is rare because of the low virulence of the infective agent. There is evidence to believe that the kidney is actually invaded and that the inflammation is not due to toxic substances carried from the distant focus of infection. Along these lines Day and Clark isolated bacilli of the colon group from the kidney in a fatal case of nephritis, and also from a case of idiopathic nephritis.

In alimentary intoxication products may be absorbed from the intestinal canal giving rise to renal complications. Certain poisons and drugs act as renal irritants. The chemical group comprises mercuric chlorid, phenol, phosphorus, lead and turpentine. The drugs may cause nephritis by prolonged administration of small doses or by the administration of a large single dose. The preparations which cause the toxic symptoms most frequently are arsenic, particularly in the form of Fowler's solution, hexamethylenamin, potassium chlorate, salicylic acid and its derivatives, ether, chloroform, betanaphthol and iodin.

(C) **Predisposing causes** are: (1) Errors of diet, especially the ingestion of excessive quantities of protein accompanied by a low water intake, (2) improper care of the skin, and (3) hereditary factors. There are well authenticated cases of nephritis occurring in several members of a family. It may be assumed that the renal tissue in a certain group or family may have an inherent susceptibility to inflammation. A mother with eclampsia may give birth to a child with kidney lesions. Congenital syphilis predisposes to interstitial nephritis. Infections in the mother may cause nephritis of the fetus *in utero*.

Exposure to cold and dampness as an etiologic factor is not clearly understood. These factors probably render the human organism more susceptible to infection from other foci in the body. This is suggested by the experimental work of Helmholz on pyelitis in rabbits. He was not able to produce pyelitis by the intravenous injection of strains of colon bacilli in these animals unless he first dampened their skin and chilled them for several hours by the electric fan.

Pathology.—Any or all of the various tissue elements of the kidney may be the seat of the pathologic lesions. When the parenchyma is involved the condition is designated as acute parenchymatous nephritis, acute tubular nephritis, or acute desquamative nephritis. If the glomeruli are affected the condition is known as acute glomerulonephritis. This type most frequently complicates scarlet fever. If the interstitial tissues are invaded, the pathologic picture is that of acute interstitial nephritis. When the glomeruli and the tubules are the seat of an exudate of leukocytes, serum and red blood corpuscles, the condition is known as acute exudative nephritis, a form which is particularly frequent in infants and young children. These lesions vary with the progress and duration of the kidney disease. Their severity also depends upon the virulence of the invading organism or its toxic products. The structural changes in the kidney are frequently out of proportion to the urinary findings as well as the functional tests.

Special Pathology.—(1) In the mild form of acute nephritis the macroscopic appearance of the kidney may not vary from the normal. Microscopic examination will indicate the extent of the inflammatory process. The microscopic changes may consist of slight degeneration of the epithelium of the straight and convoluted tubules, with congestion, as shown by enlarged vessels. In some cases engorgement of the glomeruli may be the only pathologic process present. The epithelial cells covering the tufts and lining Bowman's capsule are swollen, degenerated or desquamated.

2. In severe forms there is a decided enlargement of the kidney. If congestion predominates, the kidney may appear dark-red, and the freshly cut surface will drip bloody serum. If degenerative processes, such as occur in severe toxic nephritis, are prominent, the kidney is enlarged, pale, and on splitting, the markings are indistinct, if not entirely lost. If the degeneration is of the fatty type, the cut surface glistens, and the capsule is easily stripped from the organ. The microscopic findings vary, depending considerably on the cause of the nephritis. Interstitial proliferation or waxy degeneration are rarely found. The tubular epithelium may show various changes, chiefly those of granular or fatty degeneration. Desquamation may be present in varying degree. In severe cases the lumen of the tubules may contain red blood corpuscles, leukocytes, and broken down epithelial cells, or tube casts. The glomeruli show marked changes, particularly in the degeneration of the epithelial cells that line Bowman's

capsule and cover the tufts, and the intervening space is filled with cellular detritus, leukocytes and red blood-cells. The changes in the connective tissue are confined to a serous or fibrinous exudate. Occasionally there is an infiltration of small round-cells occurring especially in the nephritis of scarlet fever. Proliferation of connective tissue is seldom observed except in prolonged cases in which the process has passed from the acute to the chronic stage and the nephritis has changed to the productive or interstitial type.

In very severe forms there may be hemorrhages throughout the entire organ and even under the capsule, most frequently involving the tubules, the glomeruli and the interstitial tissue.

Special Forms Complicating Scarlet Fever.—The toxins developed in the course of an attack of scarlet fever have an affinity for kidney tissue. There are four recognized types of nephritis accompanying or following scarlet fever.

1. That in which the glomeruli are only slightly affected.

2. That in which hemorrhages into the glomeruli and throughout the kidney are a prominent feature.

3. True glomerulonephritis (post-scarlatinal glomerulonephritis), in which the glomeruli become the seat of marked pressure owing to the proliferation of the epithelial cells about the capillaries as well as of the capsular lining. This proliferation proceeds until the lumen of the capillaries is practically obliterated and their walls become fused with the proliferated epithelium of the capsule by means of a fibrin network. The microscopic appearance at this stage is that of a solid mass of tissue. In some instances there are no other changes in the kidney. This form probably occurs more frequently in scarlet fever than in any other condition.

4. The small round-cell infiltration form. This is not accompanied by a proliferation of the interstitial connective tissue cells, but is characterized by a marked infiltration of small round-cells, especially in the region of the glomeruli and about the blood-vessels, particularly the larger veins. There are practically no changes in the glomeruli or tubules. This condition may develop later into true glomerulonephritis in which the glomerular as well as the interstitial tissues show marked proliferation, eventually assuming the type of a chronic interstitial nephritis.

The symptomatology of Type 1 is that subsequently described under the mild form. The symptoms of Types 2, 3 and 4 are substantially the same as described under the severe and very severe forms but with certain additions. In Type 2 the urine is dark-red, brownish or smoky, occasionally simulating defibrinated blood. On boiling, the urine forms almost a solid mass of albumin, and the microscopic field shows many red blood-cells together with coarsely granular casts and much cell detritus. The temperature curve may be septic in character. Types 3 and 4, in which the glomeruli are much affected, are characterized by marked and continued edema, first of

the face, next of the legs and scrotum, and finally culminating in general anasarca. There is frequently fluid in all the serous cavities, the pleural abdominal cavity, and occasionally even in the pericardium. The blood pressure is always increased in these severe types. Glomerulonephritis usually develops in the third or fourth week of an attack of scarlet fever and may follow mild cases as well as the most severe.

Form Complicating Alimentary Intoxication.—There are alterations in the renal parenchyma, high-grade fatty degeneration of the epithelium of the convoluted tubules and cloudy swelling of the epithelium of the straight tubules, as described by Kjelberg and Hirschsprung. In some cases Czerny and Moser found localized areas of infiltration in the cortex made up of round cells or red blood-cells. Micro-örganisms were found in the exudate and completely filled many of the blood-vesels.

Form Due to Congenital Syphilis.—In congenital syphilis a diffuse interstitial inflammation of the kidneys occurs. Heller examined 13 newborn babies who had congenital syphilis and observed that the kidneys were always involved. He found a diffuse interstitial nephritis, arteritis obliterans and glomerular nephritis with hyperplasia or atrophy of the epithelium. These findings have been corroborated by many other investigators. Hecker found that the seat of inflammatory change was more frequently the kidneys than the liver. Gummata seldom occur.

Form Due to Diphtheria.—The diphtheritic toxin characteristically attacks the parenchyma as opposed to the scarlatinal poison which affects the vessels, most distinctly the glomeruli. It is peculiar as Heubner states that the convoluted tubules and descending loops and intercalary parts are very slightly altered.

Symptomatology.—Certain symptoms are present to some degree in every case of acute nephritis. These depend on the cause and extent of the injury to the kidneys and the consequent diminution in functional activity. The extent of the injury is shown by disturbances in the quantity and quality of the urinary output. Functional failure is indicated by the retention of certain substances, such as chlorids, non-protein nitrogen, urea nitrogen, uric acid, and creatinine, and is manifested clinically by edema and uremic symptoms. Since the symptoms will vary with the injury and degree of retention it is convenient to divide the types into mild, severe and very severe forms, indicating the conditions under which each occurs.

Mild Form.—In many infants and children a routine examination gives the first indication that something is wrong with the kidneys. The urinalysis will show a trace of serum albumin with an occasional hyaline or granular cast. There may be a history of lassitude, poor appetite, headaches and unusual nervous manifestations, such as restlessness, disturbed sleep, and bed-wetting with frequent desire to urinate. Marked pallor is commonly noted, and the blood findings

disclose a lowered hemoglobin percentage with normal number of red blood corpuscles. There may be slight edema of the lower eyelids.

This form is commonly associated with such infections as pneumonia, typhoid fever, tonsillitis and otitis media, and is very frequently overlooked. It is also the form which is induced by ether and chloroform anesthesia, or by prolonged medication with arsenic, betanaphthol, and salicylates.

Severe Form.—Attention may be first directed to this condition by the appearance of edema of the eyelids and extremities. The onset is abrupt, usually with fever ranging from 101 to 105°F., a rapid pulse, vomiting, marked restlessness, headache, and occasionally muscular twitching. At first there is great wakefulness but later dullness and apathy. Coma does not occur early. The urine is bloody, sometimes dark in color or, as in the nephritis of diphtheria, pale and straw-colored. It may be concentrated and scanty in amount, though seldom completely suppressed. Albumin is present early and at times in massive quantity. Hyaline, granular and epithelial casts and leukocytes are found throughout the attack. The edema rapidly becomes generalized and the serous cavities may contain considerable fluid. A pasty appearance with an expressionless look is characteristic of the condition. The eyes become watery; often the eyelids are so swollen as to close the eyes entirely. The blood pressure may show only slight variation from the normal.

This form is rarely found as a primary condition in infants and young children, but most frequently appears as a complication or sequel of one of the acute infectious diseases. It is frequent after scarlet fever. It may occur after other affections, such as tonsillitis, rheumatic fever, septicemia, influenza or other localized or general infections.

Very Severe Form.—This form is characterized by pronounced toxic symptoms. Uremic symptoms may be manifest from the very onset so that within a few hours the child is in coma. This fulminating type soon ends in death. Usually the development of uremic symptoms is more gradual. The amount of urine excreted markedly diminishes and it may be even suppressed. However, uremic symptoms may be ushered in without a considerable diminution in urine. Very soon the patient complains of intense headache which may be accompanied by visual disturbance or temporary blindness. Vomiting is marked and may be associated with diarrhea. The breath may have an ammoniacal odor, and the tongue is often furred. At this time there is marked nervousness, restlessness and even twitching. The pulse is rapid, full and of very high tension. Mental changes occur, so that at first the child seems dull, then stupid, and finally goes into coma. Convulsions may occur. They may be localized or general. A few convulsions may occur and then patient proceeds to improve. The child may pass into an eclamptic state characterized by coma and more or less persistent spasms. Occasionally there is marked restlessness and delirium. The coma and convulsions may continue until

death supervenes. If the urinary secretion is re-established, recovery may take place after a course of two or three weeks. If complete suppression has lasted longer than 36 hours, the prognosis is very grave. Children bear complete suppression better than adults, and efforts at re-establishment of secretory function should, therefore, not be relaxed even if suppression has lasted for more than 36 hours. If diuretic measures prove successful, the patient may entirely recover from the attack, but should be carefully watched for months or years thereafter with frequent urinalysis as a safeguard against subsequent attacks. The very severe type may be complicated by pneumonia, pleurisy, endocarditis, meningitis, and edema of the glottis. Fatalities may be due to these complications or to uremia. It has been suggested that albuminuric retinitis is less frequent than in adults.

General.—Hill calls attention to the small amount of albumen and the presence of a few red cells in the urine of pneumonia patients. He thinks this is caused by renal irritation. He reserves the term of nephritis for those conditions where the inflammation is more permanent.

The acute hemorrhagic form, which he defines, has for its chief characteristic a bloody urine containing a few casts. The specimen may resemble pure blood. The urine is diminished but there is no edema. Renal function is diminished, not, however, to the extent which occurs in those cases where there is edema and scanty urine containing many casts. The blood pressure is more likely normal than high. In one series it reached 140. Subjective symptoms are insignificant, and uremia does not occur in this type. The blood persists in the urine for 6 to 12 weeks, and in many cases it may be detected microscopically for several months.

The acute exudative type produces a marked edema which may be extreme. The urine is scanty at first, and polyuria develops with recovery. There is a red, heavy sediment of disintegrated blood and a large amount of albumen. Microscopically, there are large numbers of granular or cellular casts and many erythrocytes. In this form of the disease the blood pressure is usually elevated. The child must be considered to be seriously ill. There may be headache, convulsions, and occasionally a patient dies from uremia at this stage. Renal function indicates considerable impairment of kidney efficiency. If these patients recover, a chronic nephritis is likely to persist. Two of 24 patients in Hill's series died in the acute stage. In 49 cases of acute nephritis there were 25 of the hemorrhagic type and 24 of the exudative type with tonsillitis as the chief cause. It is noteworthy that in many cases of the exudative variety the etiologic factor was not definitely elicited.

DeBuys states that the symptoms in primary cases are obscure as a rule. The onset is abrupt with fever ranging from 101 to 105°F. Frequently there occur restlessness, twitching, and convulsions, vomiting and diarrhea. Acidosis may supervene. There is usually

no edema although this may appear at the close of the disease. The urine is usually scanty. In the early stages albumen may be absent though later it is found in variable quantities. Microscopically, there are hyaline, epithelial and granular casts, pus cells, renal epithelium and red cells. Anemia is a striking symptom. The course is from one to four weeks.

In the secondary type the symptoms are not well defined and nephritis may be overlooked unless the urine is examined early. The severity varies with the intensity of the original infection. Nephritis must be considered as a complicating factor of the infectious process. As a rule it does not cause death. The post-scarlatinal form is the most severe. If the urine is boiled it may coagulate to form a solid mass. In those patients who recover the active symptoms subside in two or three weeks, whereas from two to three months are required for the total disappearance of symptoms. Nephritis frequently occurs after the mild forms of scarlet fever, because prophylactic treatment is not employed. No restrictions are placed upon the diet. The child is out of bed and is permitted to play actively. He is frequently exposed to sudden changes of temperature and the surface of his body is chilled.

Berkeley and Lee studied the blood pressure in 93 cases of nephritis, of which 65 were acute and 28 chronic. They found that occasionally the blood pressure was markedly elevated in the nephritis of childhood. The systolic and diastolic pressures were not elevated to the same degree, the former averaging 20 mm. and the latter 10 mm. above the normal. The blood pressure is rarely of prognostic value, and bears no constant relation to the urinary findings. When edema is present the pressure is slightly higher.

Course and Termination.—In the mild cases of renal irritation which complicate infectious diseases, the course is of short duration. Clinical signs of kidney injury disappear in one or two weeks after recovery from the primary disease. On the other hand, if the damage to the kidney tissue is severe, the course may be greatly prolonged and extend into weeks or months. The average duration of the active symptoms where recovery takes place is about three weeks. Improvement is usually gradual; the urine increases in quantity, the edema slowly subsides, the urinary nitrogen gradually returns to normal, and the albumen and casts disappear. It may be weeks or months after all clinical symptoms have disappeared before the urine is free from albumen and casts. The nephritis sometimes disappears suddenly. Occasionally a scarlatinal nephritis is observed which shows a trace of albumen and no blood or casts, though in the third week such patients may become suddenly ill with alarming symptoms of inspiratory dyspnea, hoarseness, difficulty in swallowing and edema of the epiglottis. Death not infrequently occurs.

In a considerable number of nephritic cases, complete recovery does not take place, and the condition becomes chronic. There is

sometimes a latent phase after the acute symptoms have subsided and one is led to think that a complete recovery has occurred. In a shorter or longer time symptoms of chronic nephritis manifest themselves.

Heubner finds that 10 per cent. of the patients with acute nephritis develop the chronic form of the disease. The fatal cases almost invariably develop uremia, which may occur early in the disease and dominate the entire course. Within 36 hours the patient may be in deep coma from which he cannot be aroused. In other children uremia gradually develops as the suppression of urine becomes more complete. In the prolonged cases death may result from intercurrent infection as pneumonia, pleurisy, edema of the glottis or lungs, and occasionally pericarditis or endocarditis. Streptococcus infections tend to produce the severest forms of nephritis.

Prognosis.—The prognosis is favorable when there is no suppression of urine, uremia or other complications. This holds true particularly for children above three years. As a rule the younger the patient the more unfavorable is the prognosis. The prognosis of the acute hemorrhagic form is good as a rule while the acute exudative type with edema is not so favorable. Some mild cases protract for a few months and become chronic, while others with pronounced uremia may recover rapidly. An important question to be answered relates to the frequency of chronic nephritis following acute attacks. It is stated that six out of seven cases of acute scarlatinal nephritis recover completely. James found that 13 per cent. in a series of 67 cases developed chronic nephritis. He concludes that a child must not be considered well until several urinary examinations have been made. He should have lived under ordinary environment and on a regular diet for a considerable period. If the urine continues to be chemically and microscopically negative, it may be reasonably supposed that a cure has been effected. James studied his patients years after recovery and found that a kidney which has been injured previously is no more susceptible to intercurrent infection than the normal. Wittich regards the prognosis as serious when disturbed chlorid equilibrium, persistent edema, stationary urinary output or diminution continues. A positive chlorid balance, which implies a marked retention of these salts in the tissues, is unfavorable. A regular pulse with increased tension is favorable while low blood pressure and arrhythmia are bad prognostic signs because there is always the possibility of fluid in the large serous cavities and cardiac dilatation.

Treatment.—Prophylaxis.—Attempts should be made to protect the kidney against injury during an attack of acute infectious disease. These measures should be continued until convalescence is fully established. Maintenance and increase of the urinary secretion will aid the elimination of the toxins and will lessen their injurious effects on the renal excretory apparatus. This is best accomplished by free ingestion of plain or alkaline water and, if necessary, by the admin-

istration of a non-irritating diuretic such as potassium citrate or acetate. The use of any drug that tends to irritate or throw an additional burden on the kidneys invites disaster and should be rigidly avoided. The functional capacity of the kidneys may be spared by stimulating other excretory organs, for instance, by producing evacuation from the bowels by the use of saline laxatives and by encouraging elimination through the skin by warm sponging, tub baths and flannel coverings. Such supplemental excretion should not be pushed to the point of depletion and concentration of the urine. In scarlet fever prophylactic measures should be instituted for at least three or four weeks even in the mildest attacks. The etiologic relation of sudden chilling of the body to nephritis has been made light of by some authors. Nevertheless, it is wiser to adopt precautions that are based on a recognition of the possible injurious effect of cold on the surface of the child's body. Kerley states that if every case of scarlet fever were treated as though nephritis were expected there would be comparatively few cases.

Active.—Any course of treatment of acute attacks should consider the pathologic processes taking place in the kidney and should avoid over-burdening the organ. Mild cases of acute nephritis tend to spontaneous recovery, consequently, active medication is not required. Hygienic management should include rest in a warm bed, protection from drafts of cold air and daily bathing.

Dietetic.—The kidneys should be spared their usual work as much as possible. Fluids, proteins and salts should therefore be reduced to the minimal bodily requirements. The young child requires about 1.5 gm. of protein per kg. body-weight to keep itself in nitrogen equilibrium. The following tabulation shows the daily protein requirement and the caloric need of children at various ages:

4 years—minimal protein 30 gm.; minimum calories 1200
8 years—minimal protein 35 gm.; minimum calories 1400
12 years—minimal protein 45 gm.; minimum calories 1600

Practically 1.5 to 2 gm. per kg. is satisfactory. Hill points out that this can be obtained as a rule by omitting meat, eggs, fish and meat soups from the diet and substituting cream, milk, cereals, bread and potatoes.

The Karell treatment has been used in children. The quantity of milk is reduced to 20 ounces, and no other fluid or solid food is administered. The quantity is divided into four portions. There is usually a marked complaint of thirst. If the child is old enough he may be permitted to rinse his mouth with water. For urgent hunger he may be given a small piece of dry toast or zwieback. The patient must be kept in bed. Evacuation of the bowels should be promoted but without saline laxatives which require water. Such symptoms as dyspnea, oppression, restlessness, rapid, weak pulse or active uremic signs should be actively combatted on their first appear-

ance. The improvement under the Karell management is due to the absolute rest in bed, the low salt content, and the low fluid and food intake which gives a minimum amount of work for the body to perform.

If edema is absent a salt-poor diet may be given. This means that the bread and butter need not be salt free, and it is unnecessary to omit it when cooking vegetables and cereals. However, its free use should be prohibited. In cases of edema it is restricted because it is supposed that water retention is secondary to salt retention. A salt-free diet consists of unsalted butter and bread, cereals, and vegetables cooked without salt. This, together with free catharsis, assists in ridding the body of edema. As much as 48 ounces of water may be given daily if there is no edema. If the urinary output is less than two-thirds of the intake and the child gains in weight, the quantity of water should be reduced. Where edema is present, a reduction of the quantity of fluid below 12 ounces causes suffering from thirst. In ordinary weather most children will be comfortable with 15 to 20 ounces of water. If there is no increase in body-weight this quantity may be increased.

In general the diet should be made up largely of cereals, gruels, fruits and fruit juices with sugar, vegetable purees, rice, tapioca and farina cream custards. These are preferably prepared without salt, particularly if edema is present. This form of diet is chiefly carbohydrate. Bratke, for instance, has employed a diet made up entirely of carbohydrate for the treatment of acute diffuse glomerulonephritis. From 150 to 200 gm. of lactose may be given to children with the addition of fruit juices during 24 hours. This may be continued for two or three days without additional food, after which the diet of vegetable, fruit and cereal may be resumed.

Medicinal.—Elimination by the kidneys should be encouraged. If the urine is highly acid, small doses of potassium citrate, 20 to 30 gr. a day, with sodium bicarbonate, 10 to 30 gr. a day, should be prescribed. In mild cases this alkaline diuretic treatment is sufficient to bring the urine to normal acidity, color and quantity.

Elimination by the bowels is next in importance. In infants this is best accomplished with milk of magnesia, and in older children with citrate of magnesia. At least one good evacuation should be obtained each day. Other cathartics which do not irritate the kidneys are cascara, rhubarb, and compound jalap powder.

If the renal function is persistently low, diuretics such as theobromin sodium salicylate and theophyllin may be given. These are supposed to be preferable to caffein which is said to cause constriction of the renal vessels. Five grain doses of these drugs may be used for children of 10 years. Theophyllin probably acts by lowering the renal threshold for chlorids, allowing them to pass out of the plasma. In this way, the water elimination is increased. For the associated anemia occurring during convalescence, Basham's mixture or any suitable iron preparation may be administered. As soon as the urine has cleared and the other symptoms of mild nephritis have disappeared,

the child may be allowed out of bed and permitted to take moderate exercise in favorable weather.

Treatment of Severe Cases.—The first indication in the treatment of severe cases is increased elimination through the skin and intestines to relieve the kidneys of as much work as possible. The primary efforts should be directed to reducing the edema, increasing the urinary output, and maintaining nutrition. Elimination through the skin is encouraged in three ways: (1) By hot pack; (2) by hot air baths; (3) by diaphoretics.

The first is the most satisfactory method with infants and young children, the second is more applicable to older children who are water-logged and when handling the patient is difficult. Either method may be equally effective. Care should be exercised in keeping the child warm after it has been subjected to the hot pack or hot-air baths, by wrapping it in blankets, as a sudden chilling will counteract the benefit sought from these therapeutic measures. The hot baths should be continued until free diaphoresis is obtained, and may be repeated two or three times a day, depending upon the patient's response. The use of tincture of aconite as a diaphoretic is recommended in febrile cases and to maintain diaphoresis between packs, doses of not to exceed from one-half to one minim every two hours. While the subsidence of edema is desirable, the elimination of fluids from the tissues does not necessarily diminish the tendency to uremia.

Intestinal elimination may be effected by means of high colon injections of sterile water. Usually a pint at a temperature of 110°F. is injected with the child placed in the best position for retention. Smaller amounts may be tried if the larger quantity is too quickly injected; infants may be able to retain only three to four ounces. The saline solution may be introduced into the colon by means of a Murphy drip apparatus, but as the constant insertion of the tube tends to irritate the rectum, the persistent use of this method is frequently impossible. If the fluid so administered is absorbed, it assists in re-establishing the flow of the urine. It has been suggested that the heat of the fluid, which passes close to the left kidney, tends to increase the functional activity of that organ. The ejected fluid carries with it such waste products as may be excreted through the intestinal mucosa. Thus in a threefold way the water enemas aid in elimination. The edema may be further diminished by the use of saline cathartics, provided the patient's strength is not too greatly depleted; such a procedure is, as a rule, suitable only in older children.

The diet should be that outlined under a discussion of the treatment of mild cases, or a salt-free or milk diet. If gastric symptoms are prominent and the patient is unable to retain solid food, nutritive enemata of milk, peptonized for from 10 to 15 minutes, should be given at six-hour intervals in such amounts as will be retained.

Cardiac stimulants are not only of no value but may be positively harmful, as will be readily apparent if the pathology of acute nephritis

is carefully considered. There are, however, certain procedures aimed directly at increasing the kidney activity which are permissible. These include (1) the application of heat to the loins by means of flaxseed poultices, (2) dry cupping the lumbar region, and (3) counter-irritation over the kidney by means of fomentations.

Treatment of Very Severe Cases.—The main indication in the treatment of very severe cases is to combat the uremic manifestations which are the dominant feature of this type. In addition to continuous efforts aimed at a reduction of the edema and the reestablishment of urinary secretion, as outlined under the foregoing paragraphs, it is necessary to be on constant watch for uremic convulsions and to be prepared to act promptly when the first signs of this complication appear.

The most prominent symptoms ushering in a uremic attack should be combatted as they arise. The high tension pulse calls for nitroglycerin by hypodermic injection, to be repeated every hour for four or five doses, if necessary; for infants up to six months, $\frac{1}{400}$ gr.; up to one year, $\frac{1}{300}$ gr.; for children of three years, $\frac{1}{200}$ gr.; of five years, $\frac{1}{100}$ gr. may be employed. Attacks of vomiting necessitate the withholding of all food by mouth and feeding by nutritive enemata. The delirium and marked restlessness may be controlled by chloral, at times by codein or morphin. Complete suppression of urine calls for heroic measures to maintain the elimination through the skin and intestines. Venesection and spinal puncture are recommended as prophylactic measures in impending uremia.

A further word of caution may not be out of place. Irritating diuretics should be avoided because they may increase kidney irritation and diminish the possibility of establishing urinary flow. If the cardiac force is weak and the beats intermittent tincture of strophanthus, two to three drops every two hours for children of from three to five years; one-half of that dose for children under three years may be given.

The uremic convulsions are best controlled by chloroform anesthesia or by chloral and bromids given by rectum; twice the amount ordinarily given by mouth. The medicaments are best retained when incorporated with mucilage of acacia or with skimmed milk not to exceed two ounces. They may be repeated every four or six hours, or oftener, if necessary. In extreme cases that do not yield to these measures, venesection may be performed, five or six ounces of blood being withdrawn from a child five years of age. Intravenous injections of saline solution, of about twice the quantity of blood withdrawn, have a marked stimulating effect. In infants with open fontanelle, fluid may be injected into the longitudinal sinus. Puncturing the skin to permit the edematous fluid to escape has been recommended but is not devoid of danger. Spinal puncture during the convulsions has a beneficial influence in controlling the seizures and headache.

Surgical Procedure.—Edebohl's operation involves the stripping of the capsule from the kidney. Permanent cures have been reported

in a few cases following operation, and prolongation of life has been effected in a number of cases. The addition of months or years of life in apparent health is sufficient to justify the operation in those cases that do not prosper under medical treatment.

The theory upon which Edebohl's operation is performed is that the increased blood supplied to the kidney as a result of the operation leads to the gradual absorption of the interstitial or intertubular inflammatory products and exudates. This frees the tubules and glomeruli from external compression, constriction and distortion, permitting the re-establishment of a normal renal circulation. As a result of this improvement, there is a regeneration of secretory epithelium. The new capsule that forms is thicker and more adherent, and there is little evidence of new vessels extending down into the kidney. Morse emphasizes that the engorgement in the acute inflammation of the kidney reaches a point where excretion of urine becomes impossible. The marked tension is adequately demonstrated by the marked bulging of the kidney through the capsular incision. In this manner the compression of the tubules and impediment to free circulation of the blood is removed. It is also suggested that the manipulation of the kidneys may be responsible for the improvement.

The decapsulation with its relief of tension in no way alters the essential character of the nephritis. In a word, Edebohl's operation is thought to relieve the congestion within the kidney and may afford symptomatic relief, though the pathologic changes of the kidneys remain practically unchanged. In conclusion concerning this operation, Morse states that decapsulation should be undertaken when there is acute nephritis with marked diminution of urine and symptoms of intoxication. Then it may be a life-saving operation.

Convalescence.—In mild cases, recovery should be complete before the child is permitted to be up and about. An iron tonic is usually recommended for the accompanying anemia. The convalescence from the severe and very severe attacks is slow. The patient has little strength, the tissues resume their functions slowly and the blood volume is diminished. On account of the weakened condition of the child, drafts and chilling should be avoided. If blood reappears in the urine, the child must be returned to bed. As improvement proceeds, the appetite and color gradually return to normal. Children convalescent from severe attacks of nephritis do not withstand the rigorous winter in the northern states, and distinct benefit will be derived from a stay in milder climates, as Florida or California. The urine should be repeatedly examined for a year and foci of infection should be eradicated to lessen the possibility of reinfection.

CHRONIC NEPHRITIS

Chronic nephritis is seldom seen in infancy except as an accompaniment of some congenital malformation. In childhood it frequently

follows an attack of acute nephritis although congenital syphilis and prolonged sepsis, particularly that accompanying bone or joint disease, may produce a chronic renal disease without evidence of a preceding acute stage. There are two fairly well-defined pathologic entities: (1) Mainly parenchymatous and degenerative, and (2) interstitial productive as found in congenital syphilis, tuberculosis and endocarditis. Chronic nephritis is a frequent sequel of congenital syphilis.

Langstein and Benfey classify chronic nephritis as follows:

1. Chronic hemorrhagic type which is nearly always associated with edema. This is the most common and characteristic type for children.
2. Edema without hematuria. The urine contains a large amount of albumen and casts. Infection is not so frequently the etiology of this form as of the first class.
3. Chronic interstitial nephritis of the adult type.
4. Parenchymatous type secondary to pyelitis.
5. An insidious type in generally debilitated children following scarlet fever and tonsillitis.
6. A type associated with intermittent albuminuria which is rare.

An etiologic classification has been formulated by Blackman:

Infancy
- Gastro-intestinal
- Other infections
- Syphilis

Children
- Scarlet fever and diphtheria
- Other infections
- Cold, exposure, drugs

Congenital cases

Cases with infantilism

Etiology.—Chronic nephritis is usually secondary to disease in some other part of the body, although there are undoubted cases in which the nephritis has been primary. Chronic nephritis is a frequent sequel of the acute nephritis produced by scarlet fever or tonsillitis. Other causes are congenital syphilis, chronic endocarditis and chronic infection accompanying bone and joint disease of tuberculous or other origin. It has been maintained that the evidence is not sufficient to prove that scarlatinal nephritis is a fore runner of chronic interstitial nephritis as seen in adults. Of 281 cases of scarlatinal nephritis reported by Still, 54 per cent. were cured in four weeks, and only 24 had albiuminuria after six weeks. Rosenfeld and von Rechtenstamm examined 93 adults who had had scarlatinal nephritis in early life, 53 of whom had albuminuria when discharged from the hospital, but did not find a single case of severe nephritis. Hill states that of 30 cases of chronic nephritis which he studied only four followed scarlet fever, and he quotes Ehrenberg who found normal urine in 40 adults who had had acute nephritis before 15 years of age. Pepper

and Luke conclude that there is probably no relationship between acute nephritis of young life and adult nephritis.

Emerson points out that chronic nephritis represents repeated attacks. He states that the patient does not suffer from one attack of nephritis but from one thousand and one. A disease like scarlet fever may start the inflammation, but the repetition of attacks is due to some active factor which continues the process. Active nephritis may be caused by such lesions as infected tonsils, teeth abscesses, ulcerations or infections of the bowel. Infections of the mouth, teeth, nose and tonsils are especially important in the production of nephritis. Lesions of the skin have a special tendency to produce kidney diseases. Acute nephritis may follow slight chilling or wetting of the skin, and is also associated with various skin rashes. The treatment by sweating does not owe its beneficial effect so much to the direct elimination of any toxin or urinary constituent as to its effect on the skin and its functions. The same is true of the bowel. The intestinal wall is an external membrane. The value of purging is not only due to elimination, but also due to the improvement in the condition of the bowel wall itself. As evidence that focal infections are important in the etiology of the kidney inflammation, Rosenow found that some strains of streptococcus, particularly those whose virulence was increased by animal passage, when injected intravenously showed a striking localization in the kidneys. Some of these strains were obtained from infected tonsils and teeth. Along these lines Meisser and Bumpus showed that an organism from non-vital teeth without active infection caused pyelonephritis when injected intravenously. These facts lend credence to Emerson's contention that the foci of infection may play an important rôle in maintaining kidney infections to the point of chronicity when once an acute nephritis has occurred. The last-mentioned investigators succeeded in producing disseminated nephritis in dogs. They devitalized their teeth and simultaneously infected the pulp chambers with various organisms. Chronic nephritis, especially in cases without edema, is a localized kidney lesion associated with general disturbances.

Pathology.—The pathology varies with the type of chronic nephritis. The symptoms cannot be accurately correlated to the pathologic anatomy of the organ. Emerson states that there are two processes at work. One is a permanent element consisting of cell proliferation and scar tissue formation, both of which are evidences of healing, and the other is an acute injurious element which perpetuates the disease and indirectly increases the permanent lesion. As a rule, acute exacerbations follow each other too rapidly to allow the slightly injured renal elements to undergo complete repair.

Chronic parenchymatous nephritis may occur as the hemorrhagic form or the form associated with the "large white kidney."

The chronic hemorrhagic form is the characteristic type of chronic nephritis in children. The kidneys are large, yellow and studded with

many small hemorrhages. This type occurs after scarlet fever. The organ is dark-red, and the capsule is adherent. Bloody serum oozes from cut surfaces. Microscopic examination reveals engorgement of the blood-vessels, hemorrhages into the glomeruli, and occlusion of the lumina of the tubules with red blood cells. Such an organ soon becomes the seat of interstitial proliferation, and the picture changes to that of true interstitial nephritis. This type is associated with blood in the urine for a long period of time. There is nearly always edema, and the condition may continue for years. In some the heart is enlarged, and the blood pressure is high.

In the "large white kidney" the organ is sometimes twice the size and weight of the normal organ. The capsule strips readily, revealing a smooth surface. The cortex is thickened and has a pale-yellow appearance. The markings are indistinct; the pyramids may be separated from the cortex by the dark-red color in the former, as contrasted sharply with the pale-yellow of the latter. The glomeruli stand out clearly, being sharply defined on the cut surface as tiny gray points. Microscopically, the most striking feature is the marked fatty degeneration of the tubules with much desquamation. The glomerular changes, of the kind previously described under acute nephritis, are present and there is an infiltration of small round cells around the glomeruli and large veins. There is evidence of beginning proliferation of the interstitial connective tissue. Where the process is most advanced there is marked compression of the tubules and glomeruli as these are caught in the meshes of the connective tissue. This process may result in a secondarily contracted kidney if the disease is sufficiently prolonged. Usually this type has a shorter duration than the hemorrhagic form, and the patients die after a few months. In nearly all, the blood pressure is normal.

In chronic interstitial nephritis the pathologic process may begin as a true interstitial proliferation or it may be superimposed on a parenchymatous process, leading to the condition known as "secondarily contracted kidney." The pathologic changes in the end are quite similar, although the clinical course of the two forms may differ widely. The picture is that of an atrophied kidney often only half the size of the normal organ. Its capsule strips with difficulty, in places being completely fused to the cortex. The cut surface of the kidney is roughened and the cortex is attenuated. Microscopic examination shows the interstitial tissue everywhere proliferated and replacing the parenchyma. The tubules are compressed, and in whole areas even lacking. The tissue of the glomeruli are fused with the surrounding tissue into solid masses. Councilman describes two types. (*a*) In one there is little disturbance of renal function. The interstitial tissue is infiltrated by round cells, plasma, cells and lymphocytes. The glomeruli may not be involved, and the tubules show little degeneration. This resembles the early picture of the true contracted kidney with characteristic fatty degeneration of the tubules which are slightly

compressed. The lumen is filled with hyaline and granular material, and the glomeruli show ony a few changes. (*b*) In the second type the glomeruli are involved. They are considerably swollen and nuclear because of the proliferation of the capillary endothelium. There are many leukocytes in the capillary loops. Hyaline and other thrombi often occlude the capillary lumen and render the loops bloodless. Exudation of fibrin, cells and debris often occurs within the capsular space. The capsular lining often proliferates forming a crescentic outgrowth to which the diseased tuft becomes adherent. In another form of chronic nephritis amyloid degeneration predominates. This is usually associated with enlargement of the spleen and liver, ascites, diarrhea, and cachexia of an alabaster type. It is dependent on long standing processes, such as osteomyelitis, general furunculosis and tuberculosis. The kidney is enlarged and glistening, and its capsule strips readily. In cut sections the deposits of amyloid material may be found in the vicinity of the small arteries and about the glomerular tufts. These deposits may be differentiated by the use of tincture of iodin spread over the cut surface, a mahogany dark-brown appearance marking the deposits.

In interstitial nephritis as in adults, children have high blood pressure, hypertrophy of the left ventricle, large quantities of urine of a low specific gravity, and sometimes albuminuric retinitis.

Symptomatology.—In cases of nephritis of long standing, there are periods during which a marked anemia with characteristic pallor and considerable albumen, leukocytes, epithelial cells and hyaline, granular and fatty casts in the urine. These are the only signs on which to base a diagnosis other than possibly a history of an acute attack of nephritis at some previous time. Intervals of comparative health may be suddenly interrupted by a quickly progressing edema, which may be limited to the eyelids, hands, ankles and genitals, or may also affect the body cavities. There may be a moderate rise in temperature, marked nervous irritability and headaches, sleeplessness, loss of strength, dyspnea, vomiting, and diarrhea. Often effusions into the pleura, pericardium or abdominal cavity add a great burden to an already overworked heart. Cardiac hypertrophy has resulted because of repeated acute exacerbations. These patients are often seen in a hospital practice, as they are admitted repeatedly, each time with less vitality, until at last response to treatment of any kind fails and they "drown in their own effusions."

In intervals between attacks in chronic parenchymatous nephritis only a trace of albumin and only a few casts may be found in the urine. During exacerbations albumin in large quantities (the urine boils solid) and casts of all kinds, particularly hyaline, granular, and epithelial, are present. The specific gravity of the urine is usually normal or quite high. The urine is not at all or only slightly diminished in quantity. If waxy casts are found, search should be made for a "pus pocket" or waxy degeneration elsewhere, particularly if there is

cachexia accompanied by the peculiar alabaster appearance of the skin. The heart is not enlarged (cardiac hypertrophy indicates interstitial involvement), and the blood pressure is not increased. During intervals between exacerbations there may be virtually no symptoms whatsoever. These children are frequently thin, pale, and often show a lordosis. There is rarely edema. They are feeble and easily fatigued. In such children there may be severe damage to the kidneys while the phenolsulphonphthalein test and blood urea may be quite normal.

Chronic interstitial nephritis is characterized by relatively little edema but marked circulatory disturbances. The onset is insidious and is often unsuspected until the disease is well advanced. Early symptoms are indefinite and frequently misinterpreted. The child awakens with headache and crying and soon vomits. The attack may last 12 to 24 hours, during which time he is fairly comfortable save for occasional headache. The urine is increased in amount, of low specific gravity, 1.001 to 1.008, with a faint trace of albumen or none and an occasional hyaline cast. There is only slight edema although occasionally it may be marked. Vision is poor due to albuminuric retinitis. The heart is slightly enlarged, the second aortic sound accentuated, and the blood pressure is elevated. There may be dyspnea of the asthmatic type. The most striking feature of many of these cases is an associated infantilism. The child is under-developed mentally and physically. The course of these cases is short. Death usually occurs early. This type is not due to syphilis.

Course.—The course of each form of chronic nephritis covers from two to many years, depending upon the degree of damage and the care and treatment. The parenchymatous variety is featured by many exacerbations, recovery from each of which is more prolonged and less satisfactory than the preceding attack, until at some period all remedies and methods lose their efficacy. The lesions may slowly develop into those of interstitial nephritis, edema increases, and uremia finally closes the scene. In the interstitial form the course is characterized chiefly by headache, nervous symptoms, anemia and visual disturbances, or the disease may run for years without any acute attack, until suddenly, without previous warning, acute uremia, or more rarely cerebral hemorrhage, may result in death. The majority of these cases pass out of the hands of the pediatrician and become the problem of the internist.

Functional Tests.—Determination of renal efficiency is a more reliable index of the degree of kidney involvement than physical signs. Renal efficiency may be measured from a consideration of the composition of the urine and the composition of the blood. Certain substances should be present in the urine and other substances are retained in the blood if renal excretion is impaired. For many years the excretion of urea was considered the best guide for determining the functional activity of the kidney. Sodium chlorid has also been

used as a unit to measure the ability of the kidney to excrete certain substances usually present in the food. The excretion of salt and urea has been found to vary considerably being dependent on conditions not related directly to the actual functional capacity of the kidney tissue.

Quantity of urinary output varies considerably under physiologic conditions, depending on fluid intake, perspiration, exercise and other factors such as external temperature and humidity. Jenning's table quoted by Ratchford follows:

First year	400 c.c.
Second year	450 c.c.
Third year	500 c.c.
Fourth year	550 c.c.
Fifth year	600 c.c.
Sixth year	650 c.c.
Seventh year	700 c.c.
Eighth year	800 c.c.
Ninth year	900 c.c.
Tenth year	1000 c.c.

The phenolsulphonphthalein test of Rowntree and Geraghty is based purely on the rapidity with which the kidney tissues excrete a foreign dye stuff, phenolsulphonphthalein. The test is an index of elimination only and indicates the function at the time the kidney is studied.

The test is carried out as follows: The patient is given several glasses of water (about 350 c.c.) in order to stimulate free urinary excretion. About half an hour later a catheter is inserted into the bladder under aseptic precautions. Six milligrams of phenolsulphonphthalein (1 c.c. of 0.6 per cent. solution) is injected subcutaneously, intravenously, or, preferably, intramuscularly into the lumbar muscles. The urine is allowed to flow into a test tube containing several drops of a 25 per cent. solution of sodium hydroxid until the first faint pink tinge is noted. Then the catheter is removed and the urine is collected by spontaneous micturition at two intervals of one hour each, each sample in a separate vessel. The urine is rendered strongly alkaline with a 25 per cent. solution of sodium hydroxid to bring out the characteristic color, a purple-red. It is next diluted to 1000 c.c., filtered, and compared with a standard in a Duboscq or other colorimeter, or with standard solutions (up to 60 per cent.) or phenolsulphonphthalein in test tubes.

After an intramuscular injection, with unimpaired kidney function, from 45 to 70 per cent. of the drug is excreted during the first hour, and from 10 to 30 per cent. during the next hour. After subcutaneous injection, the excretion during the first hour is about 10 per cent. less, whereas after intravenous injection 80 per cent. of the dye may appear in the urine collected during the first hour. The appearance of the drug bears a quantitative relation to the activity of the kidney, excretion being delayed according to the extent of kidney impairment.

The phthalein test is useful in certain instances. Children usually excrete 75 per cent. of the dye in two hours. Sixty per cent. should be regarded as the low limit. In one series it was found that the chronic cases of nephritis showed a greater output than the acute. This is contrary to the condition in adults. The test is most significant if the phthalein excretion is persistently low. It indicates permanent injury to the kidney even though the clinical symptoms, including urinary findings, might lead one to think otherwise, since a persistently low phenolphthalein output is rarely found in a normal kidney.

The "two-hour" renal test suggested by Hedinger and Schleyer has been elaborated by Mosenthal. It is a qualitative test of the mode of urinary function as measured by the specific gravity, salt, nitrogen and water excretion in two hourly periods during the day and a 12-hour period at night. The principle of the test depends on throwing a load on the kidneys by a full diet containing considerable protein, urine extractives, salt and caffein with a fixed amount of fluid. The purpose of the test is to determine whether the kidneys can adjust themselves by secreting a urine of varying concentration and composition for the purpose of maintaining the body fluids at a constant level. The normal kidney yields urine of medium, low or high specific gravity, according to the proportions of the fluids and solids that must be excreted to maintain the proper composition of the body fluids. The diseased kidney loses this flexibility and cannot answer the demand for more concentrated or more dilute urine. Mosenthal states that the kidney expresses its diminished power to functionate by a fixation of its power to concentrate the urine.

In children the test diet has been modified by Hill as follows:

Breakfast		Dinner	
Cereal	2 tablespoons	Chopped meat	2 tablespoons
Bread	1 slice	1 egg	
Butter	½ cube	1 potato	
Applesauce	2 tablespoons	Butter	1½ cubes
Milk	6 ounces	Milk	6 ounces
Water	4 ounces	Water	4 ounces
Extra salt	1 gm.	Extra salt	1 gm.
Caffein sodium benzoate	2 grains	Caffein sodium benzoate	2 grains

The supper is the same as breakfast. It is not necessary that the child eat all or that the amounts should be weighed and measured. The principle is to give 10 ounces of fluid. Caffein is given instead of tea or coffee in the adult diet.

The urine is collected at intervals of two hours from 6 a.m. to 6 p.m., and the night urine is collected from 6 p.m. to 6 a.m. The program is as follows:

6:00 a.m.	Void and discard the urine
6:00 a.m.	Eat breakfast
8:00 a.m.	Void urine and place all in the labeled bottle
10:00 a.m.	Void and save as before in separate bottle
11:00 a.m.	Eat dinner

12:00 Noon. Void urine and save separately
2:00 p.m. Void urine and save separately
4:00 p.m. Void urine and save separately
5:00 p.m. Eat supper
8:00 p.m. Void urine and save separately
6:00 a.m. Void urine and save separately adding all urine voided between 8:00 p.m. and 6:00 a.m.

The specific gravity of each two-hour specimen is determined, and the amount of night urine is measured. The normal response is a variation in amount, specific gravity, sodium chlorid and nitrogen concentration of the two hourly specimens, a relatively small amount of night urine with high specific gravity about 1020 and high nitrogen concentration about 1 per cent. Normally there should be a variation of eight or more points in specific gravity and 500 c.c. or less of night urine, and a maximal specific gravity about 1.018. Lowered maximal specific gravity, fixation of specific gravity within a markedly smaller range than eight points, and nocturnal polyuria to over 600 c.c. indicates impaired renal function.

The determination of the specific gravity is most essential, but in most cases the day and night urine is also measured. In some the nitrogen concentration of the night urine may also be determined. The test is easy to carry out clinically and is of value as it gives the earliest indication of diminished efficiency and determines the maximum degree of impairment of renal efficiency before the other tests.

A similar test is one devised by Hymanson. The patient is given dry food for the entire day without cereals or fluids. The day and night urines are collected separately. Normally there is a diminution in the amount of urine secreted and a marked increase in the specific gravity to 1.030 or over. With impaired renal efficiency the quantity of urine is considerable, and the specific gravity seldom rises above 1.010. The author of this method finds this test of value in prescribing the diet and fluid allowance.

The ability of the kidney to eliminate salt and urea may be determined by administering definite amounts of these substances. The child is given a standard diet as follows according to Hill's modification:

Oatmeal	4 tablespoons
Bread	3 slices
16 per cent. cream	4 ounces
Salt free butter	2 ounces
Sugar	4 drams
Water	34 ounces
Milk	16 ounces
1 orange	
1 small baked potato.	

This diet contains about 5.7 gm. of nitrogen. On the third day of this diet the 24-hour output of salt and nitrogen is determined. On the fourth day 10 gm. of urea, representing 4.65 gm. of nitrogen, and 5 gm.

of salt are added. These are administered together in water in the morning. The nitrogen and salt are determined quantitatively in the following 24-hour specimen. It is obvious that the amounts after these elements are added will indicate the ability of the kidneys to excrete them. Normally there is a wide variation. Unless there is a marked reduction of excretion, the results are unimportant. Practically this test is difficult to perform in children. A feature of this test is that a diseased kidney may excrete either the salt or urea well, but rarely both, since there is usually a salt or nitrogen retention.

Efficiency of the kidneys may be determined by a study of the composition of the blood. Normally there is a fairly constant proportion of various chemical substances in the blood which is maintained by excretion of excesses by the kidneys. Chief among these substances which shed light on renal efficiency are non-protein nitrogen, urea, creatinin, uric acid, chlorid and cholesterol. Non-protein nitrogen includes all nitrogenous substances remaining after removal of proteins by precipitation. Other names applied are incoagulable nitrogen, filtrate nitrogen, rest, waste, or retention nitrogen. According to Folin there are 22 to 26 mg. of non-protein nitrogen per 100 c.c. of blood three to six hours after breakfast. Normal limits are usually considered to lie between 25 and 40. Ninety has a bad prognostic significance. Both the non-protein and urea nitrogen factors are indices of kidney efficiency, diet and protein destruction. Larkin and Levy state that the chief causes of nitrogen retention are diet, metabolic conditions which are not understood, edema with marked diuresis in which there is a tendency for the nitrogen content of the blood to increase only to return to the former level after the elimination of the fluid, and terminal conditions in which 24 to 48 hours before death there is a rise in blood nitrogen regardless of the existence of kidney lesions. In chronic interstitial and chronic diffuse cases without uremic symptoms there are normal or moderately elevated values. In chronic nephritis with hypertension the non-protein nitrogen is definitely increased, ranging from 40 to 180 mg. per 100 c.c. of blood. Patients with high non-protein nitrogen values are subject to rapid fluctuations in these values in the course of a few days. Farr and Austin, who made these observations, found that, as a rule, clinica improvement was associated with a fall of the non-protein nitrogen figures to nearly normal. Uremia is always accompanied by an increase in the non-protein nitrogen in the blood, but they could establish no constant relation between the degree of increase and the tendency to uremia. As yet there is no conclusion concerning the relation between non-protein nitrogen and prognosis. The relation of urea nitrogen to non-protein nitrogen is normally one-half, but when the non-protein nitrogen is elevated urea nitrogen is usually 70 per cent. of the total. The determination of non-protein nitrogen is more valuable than urea alone. From the prognostic standpoint over 100 mg. is usually fatal. High non-protein nitrogen figures given an indication

for protein poor diet. If the quantity is normal there need be no marked restriction of protein in the diet.

Urea nitrogen of the blood should be normally between 12 and 15 mg. per 100 c.c., and is considered grave at 65. Formerly uremia was ascribed to retention of urea, but with the development of blood chemistry it has been shown that uremia may occur without any material increase in blood urea. Urea nitrogen is normally about 50 per cent. of the total non-protein nitrogen, but as has been mentioned before, the greater the retention the greater is the tendency for urea nitrogen to constitute more than 50 per cent. of the total non-protein nitrogen. Blood urea varies and may lie within normal limits in individuals with damaged kidneys on a low protein diet. The urea concentration has a direct relation to diet. It is practically fixed on a constant diet. With a high nitrogen intake there is a relatively high blood urea, and the rate of excretion is parallel. Urea retention is the result of increased resistance to excretion of urea through the kidneys. Hill states that blood urea over 15 mg. in children is abnormal. Most chronic nephritis in children is so mild and slowly progressive that there is no urea retention. Nobecourt emphasizes that a persistent urea retention even if slight is dangerous. MacLean and de Wesselow state that a diseased kidney may pass as much urea as normal if there is an increased concentration of urea. Normally it requires 20 to 40 mg. per 100 c.c. to stimulate the excretion of urea, but in disease a greater concentration is required. The excretion of urea depends on the non-colloidal liquid part of the blood passing through the glomeruli. The greater the concentration of urea per unit of blood, the larger is the amount of urea passed into the kidney tubules. MacLean devised a test which is said to be more valuable than the determination of blood urea. This depends on taking 15 gm. of urea and 100 c.c. of water in the early morning. Two hours later the urine is collected and the concentration of urea determined. Patients with urea retention pass relatively large amounts with low concentration, while those without retention pass small amounts with greater concentration. Another method of determining the ability of the kidney to excrete urea is by means of Ambard's formula. He expressed numerically the relationship between the concentration of urea in the blood and the rate of excretion in the urine. When the concentration of urea in the urine is constant, the quantity of urea excreted in the urine varies proportionately to the square root of the concentration of urea in the blood. Austin, Stillman and Van Slyke state that urea excretion rate per unit body-weight increases approximately to the concentration of the urea in the blood and in proportion to the square root of the rate of volume output of urine or unit body-weight, as long as the volume rate remains within ordinary limits. Ambard held that other factors being equal, the rate of excretion of urea increases as the square of the concentration of blood urea, i.e., doubling the concentration of blood urea quadruples the excretion rate. Marshall and Davis

found that if plenty of water was administered the rate of excretion in normal animals is directly proportional to the concentration of blood urea. The increase in urea excretion with volume output was found to hold true only to a certain limit of volume output. This "augmentation limit" varied from 2.5 to 6 liters per 24 hour unit. Beyond this limit, rise of urinary volume to any height does not further accelerate urea excretion. Experimentally in rabbits an "augmentation limit" was found in the concentration of blood urea beyond which no further acceleration in urea excretion was possible, but for practical purposes this concentration was found to be so far above any condition met clinically that it may only be mentioned from physiologic interest.

Uric acid is present normally in quantities of 1 to 3 mg. per 100 c.c. It is approximately half exogenous and half endogenous as contrasted with urea which is chiefly exogenous. It is the most difficult substance for the kidney to eliminate. In early interstitial nephritis there is beginning retention in one element only, and that is uric acid. The values here reached 4 to 6, instead of 1 to 3 mg. per 100 c.c. Chace and Myers consider it of value in the early diagnosis of nephritis. McLester finds that the first sign of chronic nephritis is increased sugar and uric acid in the blood. Later there is a gradual increase in blood urea, and lastly, when uremia seems imminent, creatinin begins to rise suddenly.

Creatinin is retained only in advanced cases. Uric acid may occur without symptoms. Urea occupies a mid-position, but because of the ease of technique it is the substance commonly estimated in the blood. Normally there is from 1 to 2.5 mg. of creatinin per 100 c.c. of blood. As a prognostic test, over 5 mg. is invariably fatal after the lapse of a short period of time. In the terminal stage it may reach 15 to 30 mg. Values from 2.5 to 3 may be regarded with suspicion and 3 to 5 as decidedly unfavorable. On the whole, nitrogen retention is the difference between production and elimination. Creatinin is chiefly endogenous and not affected by diet. Retention of creatinin is indicative of a marked degree of impaired function since it is the nitrogen product most easily eliminated. Rabinowitch warns that to judge prognosis by creatinin it is necessary to differentiate two types. One is a gradual increase in non-protein nitrogenous elements of the blood with an increase first of uric acid, next urea, and last of creatinin as seen in degenerative changes in the kidney. The other is the sudden complete retention of all products as in acute toxic nephritis from bichlorid poisoning or mechanical obstruction as may occur in urethral stricture, prostatic obstruction, ureteral stone. In the latter there may be a high creatinin content which diminishes with relief of the obstruction. Cutter and Morse state that creatinin in the urine is unusual in adults but is a normal constituent of the child's urine. The relation between relative muscle mass and creatinin output which holds for the human organism at and beyond puberty, breaks down in children at earlier ages.

Creatin values vary from day to day. The amounts have no relation to pyrexia or other known conditions. Cutter and Morse state that creatin excretion is suppressed during loss of weight or pylorospasm, and is resumed when the weight curve rises.

Diastase content of the urine was measured in 1908 by Wohlegemuth. He recognized that the diseased kidney did not eliminate as much as normal. There is a decrease particularly in chronic interstitial nephritis. This is valuable because the average amounts in health are extraordinarily constant within comparatively narrow limits.

Chlorids should be excreted in quantities of 10 to 15 gm. per 24 hours. The concentration in the blood varies from 0.55 to 0.63 per cent. Persistently low concentration of blood chlorids indicates primary water retention, and the reverse indicates primary salt retention. In chronic nephritis the salt excretion is impaired before there is much disturbance of water and nitrogen excretion. In most patients salt and water excretion behave similarly. Nitrogen excretion is greatly impaired only in severe cases.

Inorganic phosphates are retained in the blood in a large number of cases of nephritis. Fatal cases show a rapid and progressive increase in plasma phosphates. Increases of more than ten times the maximum normal values have been noted by Denis and Minot. They believe that patients who are seriously ill, though not fatal in character, present relatively slight increases. It is evident that this fact is of interest from the standpoint of prognosis. The normal inorganic phosphate in the blood varies from 5.0 to 5.5 mg. per 100 c.c. Phosphates are used by the blood to excrete acids in the form of acid phosphates. When this is no longer possible, ammonia is called upon. The average phosphate content of the urine is 3.5 gm. with a range of 1 to 5 gm.

Carbohydrate metabolism is disturbed in many cases of nephritis. In the early stages of interstitial or parenchymatous nephritis when the general metabolism of the body is little disturbed, the blood sugar is very high, often equaling the values of severe diabetes. In cardiorenal cases with little or no renal disturbance, Williams and Humphreys state there is usually high blood sugar. In severe nephritis the blood-sugar curve after the ingestion of glucose resembles the "diabetic curve." Small amounts of sugar or none may be excreted in the urine, although the blood sugar may be 0.2 per cent. The blood-sugar curve rises slowly after the ingestion of glucose instead of a marked rise in one-half hour as normal. The fall is also gradual. The threshold in nephritis lies above 0.16 to 0.17 per cent. which is normal. Sometimes the threshold has a tendency to fall as pointed out by Hamman and Hirschman so that although the sugar first occurs at 0.17 per cent. it may continue to be excreted until after 0.1 per cent In those cases with excretion of sugar in the urine the blood sugar is inappreciably influenced by carbohydrate restriction. Williams and Humphreys state that these patients should not be subject to dietary restriction

of the diabetic. In these cases there is no quantitative relation between food intake and sugar excretion as obtains in diabetes.

Acidosis is frequently an accompaniment of nephritis. It has been shown that appropriate treatment of the acidosis will occasionally cause improvement of the underlying nephritis. All fatal cases of chronic nephritis with marked nitrogen retention show severe acidosis sufficient in some instances to be the actual cause of death. Marriott and Howland suggest that the acidosis of nephritis is due to the inability of the kidneys to eliminate acid phosphates. Normally, the kidneys excrete acid from a nearly neutral blood by the means of acid phosphates. In cases of nephritis with acidosis, these phosphates accumulate in the blood. Chace and Meyers state that the carbonates of the blood are the first lines of defense. The bicarbonate depletion may be roughly determined by administering sodium bicarbonate. Normally 5 to 10 gm. is sufficient to change the reaction of the urine, but in the acidosis of advanced nephritis there is often a deficiency of 100 gm. or more. In fact, in most cases the urine does not become alkaline until a higher plasma carbonate content is reached than in normal individuals. To neutralize the excess retention of acid phosphates the bicarbonate reserve of the body is drawn upon, resulting in a lowered carbon dioxid tension in the blood. Acidosis may be measured in many ways, the more practical of which are alveolar carbon dioxid tension determined by Marriott's apparatus, the carbon dioxid combining power of the blood measured by Van Slyke's method, and retention of alkali by the blood in cases in which the kidney is capable of rapidly excreting the excess of alkali. The normal range for carbon dioxid combining power of the blood in the adult is 55 to 75 c.c. of carbon dioxid per 100 c.c. of plasma. The acidosis of nephritis is a "retention" acidosis as Mason points out, as opposed to the ketosis of diabetic starvation and the vomiting of pregnancy. The latter is a productive ketosis due to the inability of the body to oxidize fats. In nephritic acidosis there is dyspnea due to the inability of the body to maintain the normal ratio of

$$\frac{H_2CO_3}{NaHCO_3} = \frac{1}{20}$$

This results in more ionized hydrogen in the blood than normal. The degree of phosphoric acid retention in the blood may be readily determined by the carbon dioxid tension in the blood.

Prognosis.—There is no specific guide to the prognosis in the chronic type, but it may be said that the outcome is usually unfavorable. Many patients with mild chronic nephritis recover, but they are susceptible to slight infections which may suddenly render the prognosis unfavorable. Anatomically imperfect kidneys may be compared to hearts which are slightly damaged in structure but function normally. Diseased portions may recover even if there has been considerable degeneration. Neighboring portions may hypertrophy and carry on

extra work. The life expectancy of the patient cannot be definitely stated, since exacerbations are prone to occur. Large quantities of urine with low specific gravity speak for chronic changes of a fibroid nature. Edema is a bad prognostic sign. Intercurrent infections are dangerous. Disappearance of albumen is no criterion of the severity of the case. The functional tests must all be taken into consideration. Hill states that many cases of nephritis recover even after 10 years or more of intermittent albuminuria.

Treatment.—As a prophylactic measure to prevent exacerbations all foci of infection should be eradicated. Infected teeth, tonsils and ears act as reservoirs of infection which may damage the kidneys. Infections of the upper respiratory tract should be guarded against as well as specific infections, such as measles. The old observation that chilling is dangerous should be heeded.

Diet should be liberal and should include sufficient protein to maintain nitrogen equilibrium. Practically 0.5 gm. of protein per kg. body-weight suffices. Therefore, the diet may include fish, eggs, chicken, bacon, meat, fruits, cereals and vegetables. Highly spiced foods, pickled and smoked foods should be avoided. Water is never contra-indicated. As a matter of fact, fluids should be amply supplied because of the tendency of fixation of urinary nitrogen. This should not be continued in the presence of a failing heart. Salt need not be absolutely restricted although excessive quantities should be avoided.

Medication should aim to treat the accompanying anemia, produce diuresis and evacuation by the bowels, and reduce high blood pressure. For the anemia, Basham's mixture or some suitable iron preparation may be given. Alkaline diuretics in the form of potassium acetate, potassium citrate and solution of ammonium acetate may be administered. A palatable mixture consists of acid potassium tartrate and tartaric acid, one ounce each, dissolved in a gallon of boiling water to which is added a pound of granulated sugar and flavored with oil of lemon. Mild laxatives may be employed if needed to produce regular evacuation of the bowels.

Hygienic rules protecting against chilling must be observed. These children thrive best in a dry, warm climate, living in the open air, exercising moderately. Frequent warm baths are beneficial, but cold baths should be avoided. The patient should not be in bed, but exercise to the point of fatigue is not desirable.

Active stages of chronic nephritis must be treated as attacks of acute nephritis to reudce edema and prevent the onset of uremia. Hot packs, hot poultices, diaphoretics, dry cupping, saline cathartics and colonic flushings are all useful. Because of the difficulty in producing free sweating it is often found preferable to substitute hot-air baths. It it believed that diuretics may stimulate the undestroyed portion of the renal parenchyma. At times there seems to be remarkable reduction in edema by theobromin and its related compounds. If the blood pressure is high, nitro-glycerin may be given, but its

effects must be closely watched because children do not tolerate this drug as well as adults. Digitalis preparations may be given for the cardiac and diuretic effects. The measures for uremia outlined previously are applicable here.

Two special forms of treatment merit separate consideration. One is the high protein feeding of Epstein, and the other is the decapsulation operation of Edebohls. Epstein separates one form of nephritis from all other types and speaks of it as chronic nephrosis. Pathologically this represents a tubular degeneration as the predominant process. The glomeruli are not diseased, and the tubular change is not dependent on inflammatory etiology. Clinically these cases are characterized by intense oliguria, albuminuria and edema. The albumen content of the urine may equal 50 gm. daily, while the albumen content of the blood is 210 gm., according to Epstein's estimates. The urine is free from formed elements. He claims that the blood does not accurately measure the amount of retained chlorids and nitrogen because these remain in the tissues, and only after diuresis is established do they appear in the blood in abnormally high quantities. He believes the condition is essentially a metabolic disease, related in all probability to myxedema. Reduced basal metabolism adds further evidence to this argument. He thinks of the conditions as a diabetes albuminuricus, a metabolic disorder leading primarily to albuminuria with secondary changes in the kidney. In this condition the protein content of the blood is markedly diminished and the relation of albumen to globulin is altered. Normally the protein of the serum forms 6 to 8 per cent., while the ratio of albumen to globulin is 4:2 or 5:3, the globulins forming 37 per cent. of the total protein. In this form of nephrosis the total protein averages about 3.9 per cent. and the ratio of albumen to globulin is 0.466 to 3.4 per cent., the globulins forming 89.2 per cent. of the total protein. There is also a marked cholesterinemia with cholesterol values 0.333 gm. to 1.23 gm. per 100 c.c., instead of the normal 0.175 to 0.225 gm. This constituent serves as a measure of the severity of the process, and the excess is a constant accompaniment of chronic nephrosis. He argues that the water retention and subsequent edema are extra-renal and due to the reduced amount of colloid, lowering the osmotic pressure of the blood. The conclusions are arrived at after a consideration of the possible factors in the production of edema and emphasizing the factors of osmosis. The factors in the transudate are (1) mechanical, consisting of the pressure in the capillaries, and (2) chemical, consisting of pressure exerted by the constituents of the blood and tissue fluids by diffusion and osmosis. With other factors constant if the proteins of the blood are reduced, fluids will go from the capillaries into the tissues producing edema. The protein of the blood exerts an osmotic pressure of 25 to 30 mm. Hg normally. In nephrosis the protein content may be reduced 60 per cent. to 70 per cent., reducing the osmotic pressure from 20 to 24 mm., permitting the passage of fluids into the tissues, as

described. Experimentally, edema has been produced by low protein feeding and overcome by feeding casein. From this work Epstein devised the method of feeding protein to restore the protein content of the blood. He gives a diet consisting of 1280 to 2500 calories of which there is 120 to 240 gm. of protein, 20 to 40 gm. of fat (unavoidable), and 150 to 300 gm. of carbohydrate. The articles used are lean veal, lean ham, white of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea, cocoa. The fluid is restricted to that of the food plus that amount necessary for the comfort of the patient, varying from 1200 to 1500 c.c. Salt is given where necessary for palatability. He considers the cure complete when the normal state of the blood is restored as regards cholesterol, protein and albumen-globulin ratio. He has seen many good results with thyroid feeding and is inclined to think there is a deficiency factor in this condition. Others have suggested that the beneficial effect of high protein feeding is due to the increased urea content of the blood which induces diuresis.

Edebohls' operation is of value in some cases of chronic nephritis, although theoretically its usefulness would seem to be limited to acute cases with marked congestion which is relieved by stripping the capsule. In chronic nephritis with its bad prognosis too much hope should not be held out to those for whom the capsule stripping operation is to be performed. Morse points out that the possible benefit cannot be due to relief of tension or to the establishment of a new circulation from outside the kidney. Again it is suggested that the handling of the kidney during operation may be responsible for the food affects sometimes seen. Morse found the results encouraging in 23 cases. All of them were getting worse, and all, he states, would have died in a short time. As a result of the operation apparently two were permanently cured, one was well with normal urine for nine years and one eight months. One was well for two years and died from acute nephritis not connected with the previous illness. Two were well as long as they were under observation although the time was too short to draw conclusions. Nine were so much improved by the operation or following the procedure that they have been symptomatically well for months and years, instead of the chronic invalids they were formerly. He admits these were not cured and would die some time from their disease.

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CHAPTER XCIX

THE PYOGENIC INFECTIONS OF THE URINARY PASSAGE

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PYELONEPHRITIS

(Pyelocystitis, Pyuria, Bacteriuria)

History.—Suppuration of the urinary organs, particularly of the kidney, is mentioned by most of the ancient physicians, Hippocrates, Galen, Aetius, and others. It was not until the days of Rayer, however, that a distinction was made between suppuration of the kidney proper, and that of the pelvis.

Rayer, in 1837, described for the first time the entity that is now called pyelitis, namely, the inflammation of the pelves of the kidneys. He also pointed out that the inflammation frequently spread from the pelvis to the substance of the kidney, and that from the infected kidney might arise a secondary infection of the pelvis.

Hüttenbrenner, in 1876, was one of the first to call attention to the disease in infancy and childhood. It is perhaps interesting to note his description:

"**Pyelitis.**—The inflammation of the calyx and pelvis of the kidney is a very common disease and may easily be mistaken for and treated as some other condition. Moreover, it often happens that it is found accidentally at autopsy in an illness which appears to have no relationship to it, for instance, in infants with intestinal catarrh, enteritis, and so forth. The mucous membrane of the calyx and pelvis is found injected and dilated with a cloudy, purulent urine. Upon investigation of such urine, besides the pus cells, a great amount of detached cylindrical epithelium and urates, ammonium, or phosphates of ammonium magnesia are found. It appears that the urine in many intestinal diseases acts as an irritant on the mucous membrane of the pelvis and becomes the cause of the catarrhal condition.

"If the pyelitis appears as a separate disease, vague signs precede, just as premonitory symptoms are noted in many acute diseases. It may start with vomiting so that one might think some other febrile disease was beginning.

"Children run a moderate fever continuously, the fever shows no noteworthy typical exacerbation, the pulse is accelerated, the appetite is poor, tongue coated, and there is a bad odor from the mouth. The urine is thick, not diminished in quantity, while the specific gravity is not noticeably lower, the reaction is slightly acid or neutral, albumin

is present in small amounts. The microscopic examination shows, in addition to the crystals of sodium urate, pus corpuscles in moderate number, isolated red blood corpuscles, numerous epithelial cells from the calyx and pelvis, and so forth. No renal epithelium or hyaline casts are found, indicating that the parenchyma is not affected.

"If the inflammation is merely confined to the pelvis, then micturition is almost without pain, but often the illness is associated with an acute cystitis, so that frequent spasms of the bladder occur which appear to be very painful. One recognizes a complicating cystitis by the quantity of pus and the detached bladder epithelium. Such urine contains a good deal of sediment and often one-half of it is pus. Very rarely does a parenchymatous infection develop from such an affection of the kidney. This might manifest itself through familiar signs in the urine and in early edema which is always lacking in pyelitis. Only in rare cases is there painfulness to touch in the lumbar region, or do the children complain of a dull pain in the renal region. Still not much reliance can be put upon this symptom, as older children often have pains of a rheumatic nature after gymnastics.

"The course of a pyelitis is generally favorable, no further secondary diseases arise. The duration is from eight days to three or four weeks, during which time the children should be kept in bed as long as they have a fever. Later moderate exercise in the open air can be allowed. The food should be easily digestible, as soup, milk, and fresh vegetables. Meat should be avoided for a few days. When the quantity of pus first decreases, some meats might be ordered. One should avoid all diuretics, they only irritate the kidneys. For dilution of the urine, various mineral waters in large quantities may be prescribed and during the time little of the customary drinking water should be taken. Children, who have once been ill with pyelitis, are susceptible to recurrences."

Seventeen years later Hirschsprung alluded to the ailment and in the following year, 1894, Escherich again called attention to the common occurrence of pyelitis in infants and children, particularly in girls. Because the colon bacillus was found so often as the causative agent, he called the condition colicystitis. From this designation it is seen that Escherich, and later Trumpp, considered the infection to be principally in the bladder. This view, however, on later investigation proved erroneous, and from the works of Finkelstein, Heubner, Holt, and many others, it has been demonstrated quite conclusively that, in the great majority of cases of pyuria, there is involvement of the pelvis of the kidney.

The relatively low mortality rate of pyelitis has made a study of the seat of infection difficult until recent times. With the improvement in cystoscopes, ureteral catheterization of infants became possible, and it has been shown by Hinman, Kretschmer and Helmholz, and others that in cases of pyuria there is usually an inflammation of one or both of the kidney pelves.

Definition.—Pyogenic infections of the urinary passages are manifested by the presence of bacteria and pus in the urine. The infection is usually caused by a member of the colon group of organisms, and clinically it is marked by fever, pallor, and the absence of other clinical symptoms.

Etiology.—Prevalence.—Except for common colds and gastro-intestinal disturbances of infancy, pyelitis is one of the commonest diseases of childhood. In eight years of experience, Göppert found that pyelitis made up about 1.2 per cent. of his entire practice. Smith estimates that it comprises about 1 per cent. of all cases seen by pediatricians.

Age.—Pyelitis has been rightly termed as a disease of the diaper age, for beyond the second year it decreases rapidly in frequency. In older children it is usually a more serious disease, although not nearly so common. It is most often encountered during the second and third quarters of the first year, and is rather rare in the first six months, although there is a very definite type which occurs in the first 10 days of life, as described by Smith, Kovalesky and Moro, and Helmholz.

Familial Tendency.—The general frequency of pyelitis makes it difficult to know whether there is a familial tendency to the disease. The only definite instance which has come under my observation was of a family of six, four girls and two boys. Each of the girls in turn developed pyelitis some time during the first two years of life; in each instance the disease ran a very stormy course and cleared up gradually.

Sex.—Escherich was the first to point out the great prevalence of pyelitis in girls, and various observers have described from 57 to 100 per cent. of cases in girls; Friedenwald 72 per cent.; Abt 95 per cent.; Escherich 100 per cent.; Box 95 per cent.; Göppert 89 per cent.; Thompson 79 per cent.; Still 88 per cent., and Kowitz 57 per cent. There can be no doubt that the common colon bacillus pyelitis, during the diaper age, is more common in girls than in boys. The more severe infections often associated with lesions of the kidney (cortical abscess), are as common in boys as in girls; this is true also for perinephritis. Pyelitis of the newly born infant is also as common in boys as in girls.

Seasonal Incidence.—There are two definite periods of the year when pyelitis seems to be more common; in the summer, when it is associated with gastro-intestinal disturbances, and in the winter, when it follows infections of the upper respiratory tract. The infections, whether during summer or winter, are in most instances due to the colon bacillus.

Natural Immunity.—As far as we know at present, there is no natural immunity to the disease. Its frequency as a complication of extra-urinary infection would make it appear that, only after the natural immunity of the urinary passages is lowered, is infection likely to take place.

Predisposing Factors.—These factors must be considered under two headings; (1) pyelitis which is primary in infants and children, and (2) pyelitis, which complicates a great variety of ailments affecting practically any of the other systems of the body. It must be assumed that retention is the most important factor in infection. Retention may be due to stone, valves, strictures, phimosis, or it may be functional. Chilling, exposure on auto rides, sitting on cold floors, or in drafts, are repeatedly given as the possible exciting causes. In the second type of cases, besides the lowering of resistance, due to infection, the same factors are active.

A great variety of organisms have been mentioned as causes of pyelitis. An unusual feature is the infrequency with which the gonococcus is the causal agent. The tubercle bacillus occasionally is found to be the sole etiologic factor of a urinary infection, but more often the colon bacillus is associated. In certain rare cases, no organisms are isolated by the usual bacteriologic methods. These infections are usually with the tubercle bacillus, but in rare instances they may be due to a streptothrix infection, as recently described by Cecil and Hill. Soldin and Langer believe that with the onset of pyelitis the *Streptococcus lacticus*, which is normally present in the urine, is replaced by the colon bacillus. Helmholz and Millikin were unable to confirm these observations, and found the organism in only 8 per cent. of specimens of normal urine.

In most of the work on pyelitis, cultures have been taken only from the bladder. In recent years studies of ureteral cultures have been made by Hinman, Kretschmer and Helmholz, and others, showing that the pelves of the kidney are usually infected. Thus far no serologic studies have been made to show whether the colon bacillus found in the urine is specific to the gastro-intestinal tract of the individual, or whether it gains access from the outside. Herrold has shown that colon bacilli from the feces and urine may be serologically and biologically the same. It is further of interest to know that normally the urethra does not contain bacilli of the colon group, and that the organisms that are present are usually staphylococci, or members of the pseudo-diphtheria group. Schwartz, in a study of the urine in 18 unselected cases of chronic gonococcus vulvovaginitis found only gram-positive staphylococci and diphtheroid bacilli.

In diseases of the gastro-intestinal tract, gram-negative bacilli are found frequently in the urinary passages. Schwarz found that in 63 per cent. of patients suffering from gastro-intestinal disorders there were gram-negative bacilli in the catheterized urine, and in 21 per cent. their number was sufficient to indicate a bacilluria. The bacilluria was twice as common in girls as in boys. Helmholz and Beeler found that in gastro-intestinal disturbances in the first year of life, the colon bacillus was found in the urethra in about one-third of the cases; after this age it was rarely found.

Modes of Infection.—It should be noted at the outset that the usual mode of infection in pyelocystitis has not been definitely determined. Furthermore, the primary seat of infection is not yet known, and in only relatively few cases has the location of the inflammatory process in the urinary tract been ascertained. Necropsy findings and ureteral catheterization demonstrate that the pelvis of the kidney is usually involved, but in any particular case clinical evidence is not sufficient to localize the seat of infection. Experimentally it has been shown that the upper urinary passages may be infected by way of the blood and by way of the bladder. In order to convey a comprehensive idea of the possible modes of infection, the evidence for and against the various routes will be cited somewhat in detail. Almost all writers have observed that pyelocystitis is more common in baby girls than in baby boys. From 57 to 95 per cent. of all cases of pyelitis have been reported by various observers as occurring in girls. Because of the short urethra in the female, infection of the bladder from without is supposed to be more readily effected. This led to the assumption that infections of the urinary tract were by the ascending route. The exposed portion of the female genitalia, and their constant contamination with fecal material during the diaper age, make it seem likely that the colon bacilli reach the bladder by way of the urethra. In view of this, Smith suggests that microörganisms gain entrance to the blood stream by way of the lymphatics of the external genitalia, and thence to the kidney. The same fact may serve as a basis for the theory of various modes of infection, for example: The ascending and the hematogenous. Another mode of infection, the so-called transparietal mode of Franke, is based on the existence of lymphatic anastomoses between the ascending colon and the right kidney, but there is no exact proof that pyelitis can be produced in this manner, and the mode will not be included in the discussion of the hematogenous and the ascending types of infection.

Hematogenous Infection.—In favor of the hematogenous mode of infection the following evidence may be cited: In 1896 Biedl and Kraus demonstrated that live colon bacilli and staphylococci could be eliminated from the blood stream by way of the kidney without injury to the urinary tract. It has further been shown by a number of observers that colon bacilli are being absorbed in the gastro-intestinal tract, carried into the blood stream, and either destroyed there, or excreted by the kidney.

The excretion of typhoid bacilli in the urine without infection of the urinary tract, and the occasional presence of tubercle bacilli in the urine without evidence of involvement of the kidney, are further proofs that organisms are excreted through the kidney during a bacteremia. Broek was able to demonstrate in 7 of 14 cases of bacilluria associated with infectious diarrhea, positive cultures of colon bacillus. Cabot and Crabtree demonstrated in the adult positive blood cultures preceding urinary infection with the colon bacillus. Kowitz found

the colon bacillus in the blood and urine in five cases of infectious diarrhea. Soldin and Langer reported the isolation of the *Bacillus lacticus* in the blood of eight patients with severe nutritional disturbance. On the other hand Levy has shown, in a series of 16 cases, that there may be a definite colon bacillemia without bacilluria. Lepper found that, in the rabbit, bacillemia may persist for a number of days without the appearance of bacteria in the urine. Magoun demonstrated that bacteria enter the blood stream very rapidly from an infected pelvis, particularly if there is back pressure.

The question of sterility of the urine is also of importance in this connection. If it were true, as Langer and Soldin maintain, that bacteria were normally being excreted by the kidney, it would be greatly in favor of the hematogenous mode of infection. Their experiments are open to criticism, however, because with their technique it is impossible not to carry in an occasional organism with the catheter. The work of Helmholz and Beeler demonstrated that in normal infants organisms were found only occasionally in the bladder urine obtained with proper precautions, and that the organisms were usually of the coccus or diphtheroid type. Because of their number, it was assumed that they were carried in with the catheter. Soldin and Langer, in a later study of 139 cases, found the *Streptococcus lacticus* in 128 cases; in 16 associated with colon bacillus. In the 11 remaining cases they found colon bacillus alone, and in four other cases *Bacillus lactis aerogenes*. The difference between their results and those of other observers, they ascribed to the fact that they used a liquid medium which, they claimed, was essential to the growth of the *Streptococcus lacticus*. Helmholz and Millikin in repeating their work with the same technique, were able to find the *Streptococcus lacticus* in only 8 per cent., and in only a few instances were they able to demonstrate the organism in the liquid media when it could not also be demonstrated in solid media.

It has been shown by Beeler and Helmholz, and also by Schwartz, that in parenteral infection, and in gastro-enteritis the colon bacillus is very much more often found in catheterized specimens of urine. Schwartz found that in cases of gastro-enteritis 63 per cent. revealed gram-negative bacilli.

Ascending Infection.—In favor of the ascending mode of infection is (1) the frequency with which pyelitis occurs in girls, (2) the incompetency of the ureteral valve in the bladder, and the demonstration of reflux to the pelvis even in normal persons and in experimental animals, and (3) the fact that bacteria can enter the blood stream from an infected pelvis.

The production of pyelitis in experimental animals with the colon bacillus has been rather difficult, unless there was some obstruction to the outflow of urine. The one exception to this is found in the experiments of Beeler and Helmholz with an organism isolated from a case of spontaneous pyelitis in a rabbit. With this organism they were

able to produce pyelitis in about two-thirds of the animals injected, both by intravenous administration and by injection into the bladder.

Histologically, Helmholz pointed out certain differences distinguishing the experimental ascending pyelitis from the hematogenous form. The latter was characterized by cortical and medullary abscesses, and subepithelial infiltration, particularly of the papilla. The parietal portion of the pelvis was not inflamed. The ascending form, in a number of instances, revealed marked peri-ureteral inflammation, marked purulent infiltration around the proximal end of the ureter with extensions into the peripelvic fat. The inflammation of the pelvis was on the parietal wall, and in only one instance was there an abscess of renal cortex.

There is as yet no evidence to prove that there is a distinctive patnologic lesion for ascending pyelitis, as compared with the hematogenous form, but it may be said that lesions in the pelvis when associated with cortical abscesses are likely to be of hematogenous origin. To this group belong the cases reported by Thiemich. A bacteriologic study was not made in his cases and, as he particularly points out, no lesions of the pelvis or bladder existed. It seems justifiable to assume that he was dealing with a peculiar infection, probably with a member of the coccus group, and not with the usual colon bacillus pyelitis.

The evidence thus far presented indicates that pyelitis may be caused either by the ascending, or the hematogenous route. Knowledge with regard to which infections are limited to the bladder, and which involve the entire urinary tract, is still so fragmentary that it is inadvisable to attempt to decide which is the more likely mode of infection.

Pathologic Anatomy.—Very little is known concerning the morbid anatomy of simple pyelitis. Often in long continued cases of so-called pyelitis, the pelvis of the kidney may appear entirely normal microscopically. Until pathologic material can be obtained from cases which have been controlled during life by ureteral catheterization and bacteriologic studies, it will be difficult to interpret findings. At present these vary from almost complete destruction of the kidney to an organ that appears practically normal at necropsy. In cases of simple pyelitis, in which the patient dies from some other cause, the renal pelvis shows no demonstrable changes, or only a few small ecchymoses. Unless the post-mortem examination is performed almost immediately after death, the urine destroys, to a considerable extent, the lining mucous membrane. In the severer cases there may be a thickening of the mucosa and numerous hemorrhages. In very severe cases even pseudo-membranous inflammation may be found.

The kidneys of patients dying from urinary infection by way of the blood stream may show very marked changes (Fig. 157). The lesions are generally due to a damming back of the urine and infection of the kidney substance. The pathologic picture varies with the chronicity of the obstruction, and the time infection took place. Inflammation of the

pelvis superimposed on hydronephrosis will disclose a markedly dilated pelvis with a flattening out of the papillæ, dilatation of the calices, and a marked involvement of the kidney substance. In the chronic cases there may be innumerable miliary abscesses throughout the cortex, and purulent streaks radiating upward from the papillæ. In more acute cases, the process may manifest itself as a non-purulent pyelonephritis with tremendous swelling of the kidney, fatty degeneration,

FIG. 157.—Critical abscesses. Hematogenic infection.

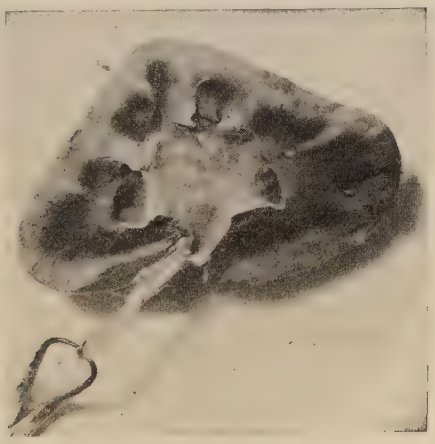

FIG. 158.—Non-purulent pyelonephritis.

and necrosis (Fig. 158). Obstruction may be due to calculi, postureteral strictures, congenital anomalies, or it may be inflammatory in character.

Histologically, simple pyelitis is characterized by the very slight changes in the lining of the pelvis. Where the cases are more chronic, there is usually a very definite increase in the subepithelial connective tissue, infiltration of the parenchyma with lymphoid cells, and a tendency for a single layer of epithelium rather than the stratified covering

of the normal pelvis. In cystitis the evidence of infiltration of the mucous membrane is usually marked, as is also the subepithelial collection of leukocytes.

Modes of Conveyance.—The direct transfer of pyelitis from one patient to another seems to be unusually rare. Huet describes an epidemic of pyelitis in five girls; the disease was supposed to have been communicated from one to the other by a night nurse.

Relapses.—Numerous observers have noted the frequency of relapses in pyelitis. Göppert recounts several instances of recurrences, even after years of apparently normal health and negative findings in the urine. Ross, on the other hand, contends that these cases are reinfections rather than relapses. In almost all articles on pyelitis, the frequency of relapses is commented on. This, no doubt, is due in large measure to the fact that the clinical symptoms disappear very much earlier than does the inflammatory condition in the urinary tract, and a sudden rise in temperature in a patient who has been free from fever and other symptoms for some time is usually considered a relapse, when in reality it is merely a return of symptoms.

There has been no large series of cases reported, in which the urine has been carefully controlled culturally before the patient has been considered cured. Almost all pediatricians seem to consider absence of foreign elements in the urine satisfactory evidence of a cure. This is not enough. Before pronouncing recovery in cases of pyelitis, it is necessary that at least two sterile cultures be taken at intervals of several days. It has been my experience that following this procedure, relapses are very infrequent.

Symptoms.—The clinical picture of pyelitis in the infant differs so much from the picture in the older child that it seems best to discuss their symptoms separately.

The disease in the infant, whether severe or mild, is characterized by the absence of any signs localizing the condition in the urinary tract. Even in the severe cases, bladder symptoms are present in less than 3 per cent. The onset is usually acute, with fever. The child may show no other evidence of illness, but in many instances a peculiar ashen pallor, an unexplained restlessness, and an anxious facial expression characterize the onset. Whether the colicky pains occasionally noted are of renal origin, or are due to secondary gastro-intestinal disturbances, is difficult to determine. Even the fever may be so slight that unless a thermometer is used, nothing abnormal is suspected. The findings in the urine alone are pathognomonic. So well established is the clinical entity of high fever, pallor, and restlessness, without other findings in the routine physical examination, that the diagnosis of pyelitis is often made before the urine has been examined.

Whether the nature of the infecting organism, or the portion of the urinary tract involved, accounts for the difference in the clinical picture is difficult to determine, but with identical findings in the urine, one patient may be apparently perfectly well except for a high fever, and

another may have very marked systemic intoxication characterized by coma, nausea, vomiting, diarrhea, and rigidity of the neck. This latter group is frequently mistaken for pneumonia, meningitis, or acute gastro-enteritis. Secondarily, there is involvement of the kidney substance, which can generally be demonstrated by enlargement of both kidneys.

Various types of fever may accompany pyelitis. As a rule, the temperature is 102 degrees, or above, often reaching 105 and 106 degrees. The fever is usually remittent; there are many variations, however, the mild form in which the temperature rarely goes over 100 degrees, and the septic form in which the temperature varies from 98 to 106 degrees. In this type, at onset and during its course, chills may occur. In certain cases, the temperature is constantly high, much as in pneumonia, and ends suddenly with a crisis. The transient blocking of the ureter may cause a sudden rise of temperature when the urine is almost free from pus; with relief from the obstruction there is a drop in temperature and a shower of pus in the urine. A similar decline in the temperature is occasionally seen in infants who have refused all fluid for a time, and are then given large amounts by stomach tube or intravenously.

As a result of the infection in pyelitis, gastro-intestinal disturbances, as well as nervous manifestations, restlessness, stupor, and occasionally stiffness of the neck, often occur secondarily.

Soldin and Langer, and Langstein and others, go so far as to claim that all cases of pyelitis are secondary. The consensus of opinion, however, is that there is definitely a group of primary as well as secondary cases. The primary group is typified by the well-developed breast fed infant who is taken suddenly ill with an infection of the urinary tract. The cases of the secondary group follow in the wake of infections of the upper respiratory tract, and the disturbances of the gastro-intestinal tract. The first group is often overlooked, because the secondary gastro-intestinal disturbances are held accountable for the febrile attack. The secondary group is more often overlooked because the urine is normal when examined at the onset of the acute illness, and is not reëxamined when the complicating pyelitis sets in.

Pyelitis of the Newborn Infant.—Pyelitis of the newborn infant is worthy of special mention because it is more common than is supposed, and has received very little attention in textbooks. It is overlooked at this time, as in later years, because urinalysis has not been performed. An unexplained fever occurring in the first two weeks of life may be due to a pyelitis.

Three of the four patients I observed, were boys, the other was a girl. The boys were infected by the colon bacillus, the girl by the *Staphylococcus aureus*, later by the colon bacillus, and finally the colon bacillus replaced the staphylococcus entirely. Three patients had no definite symptoms, and the fourth had symptoms entirely referable to the gastro-intestinal tract. The clinical picture was that of an

unexplained fever in an apparently normal newborn infant. In two instances the fever gradually increased to 104 degrees. The diagnoses were made by examination of the urine. The infection in the boys cleared up rapidly, the urine becoming sterile within three weeks. The infection in the girl persisted for more than three months.

Kovalesky and Moro have reported a case of pyelitis due to colon bacillus in an infant aged eight days, who died. Smith has reported a series of cases with favorable outcome.

Pyelocystitis in Children More Than Two Years of Age.—In children beyond the diaper age the symptoms of pyelocystitis are usually more definitely localized. Patients are often seen who have pain in the lower abdomen, burning, tenesmus, and pollakiuria; others may have a constant desire to urinate. The general symptoms may be almost entirely absent, there being little, if any fever, and no malaise, or loss of appetite. Occasionally the onset is marked with profuse hematuria.

An illustrative case is that of a child aged four years, who had recently recovered from an attack of tonsillitis, and suddenly complained of pain in the lower abdomen, and a desire to urinate every few minutes. The mother noticed small blood clots in the urine. The patient was seen the same afternoon, apparently with no complaint except pain and frequency. The temperature was 99.5 degrees. The physical examination was negative but the urine showed a large amount of pus, and numerous blood clots. Colon bacillus was isolated on culture. Complete recovery followed after a week's rest in bed, forcing of fluids, and alkalinization. At no time did the temperature rise above 100 degrees. It is possible that this was a simple cystitis without involvement of the renal pelvis, but the evidence was not definite.

The common form of pyelitis in older children is the so-called typhoidal, in which the symptoms resemble very closely those of typhoid fever for which it is often mistaken. In these cases, just as in cases in infancy, there are no symptoms that suggest a urinary infection. There is usually high fever, abrupt in onset, although occasionally, as in typhoid, it increases gradually. General malaise, loss of appetite, stupor, headache, and often delirium are present. There may be swelling of the spleen and leukopenia, or the leukocytes may be within normal limits. These patients are usually severely ill, and have a continued high fever for from two to four weeks. If there is no involvement of the kidney substance, or abnormality of the urinary tract, they usually recover completely. It may be difficult to determine the outcome by the clinical course alone, and the determination of the phenolsulphonephthalein output, and the urea in the blood is very helpful in distinguishing a case with a bad prognosis.

Report of Case.—Case 1. J. B., a child aged six years was admitted to the hospital in a very serious condition, with high fever and extreme toxemia. A diagnosis of pyelitis had been made at the

onset of the illness three weeks previously. The child had never been ill before, according to the mother's report. On a large fluid intake the urinary output greatly increased and the toxemia improved somewhat for a few days. The patient then relapsed into a semi-comatose state. The urine resembled pus from an abscess. The blood urea was 750 mg. The child died several days later of toxemia. Necropsy revealed bilateral chronic hydro-ureter and hydronephrosis, acute infective pyelonephritis, with abscess formation, and almost complete destruction of kidney substance.

A type of the condition difficult to classify is the primary pyelonephritis with large amounts of pus in the urine, and without edema and at times without pus casts involvement indicating renal. These cases are usually infections, due to a streptococcus, which may be very difficult to cultivate from the urine. Without pus casts, or edema, the condition cannot be differentiated from a simple pyelitis.

In the pyelitis of the older child the possibility of factors other than simple infection must be considered. The presence of stones, tumors, tuberculosis, strictures, and other abnormalities may account for the stasis that made infection possible, and in like manner prevents recovery from the disease.

Course and Complications.—The course of pyelitis in patients with normal urinary tracts is usually favorable. The acute symptoms may be very severe and the temperature may reach 106 degrees and remain elevated for days. It is extremely rare, however, that infants die from simple acute pyelitis. Almost invariably it is the complicating nephritis which causes death. This may occur either in the form of multiple abscesses of the parenchyma of the kidney, or as a generalized pyelonephrosis with a complete suppression of kidney activity. Renal complications are particularly prone to occur if there is obstruction to the urinary flow.

The course of the pyelitis is, in a measure, dependent on whether it is a primary infection, or secondary to some extra-urinary infection. As a rule the course of the secondary pyelitis is more favorable than that of the primary, especially in regard to their duration. There is a distinct tendency for the secondary pyelitis to abate when the primary infection subsides. On the other hand there was a very high mortality, in the group of cases with jaundice described by Rach and von Reuss, and Finkelstein.

The symptoms at the onset are no indication of the probable course of the disease, nor is there any connection between the subsidence of the general symptoms and the evidences of infection in the urinary tract. The child may appear perfectly well and still there may be as much pus in the urine for days and even weeks after the temperature has dropped to normal, as when the most severe symptoms are present. As a rule, the acute general symptoms, fever, restlessness, and lack of appetite, persist from ten days to two weeks. In the severe cases an acute course may last from three to four weeks in spite of

all therapeutic measures. Exceptional cases continue for years. There may be pus in the urine constantly and absence of fever with occasional periods of irregular fever. Other cases seem to run an afebrile course for weeks and months and then have a recrudescence. In these recurrences there may be an extension of the involvement to the kidney substance. The question of recurrent pyelitis is stressed by many authors, but in no series has urine been found sterile on repeated examinations. It seems much more probable that in these cases one is dealing with recrudescence and not recurrence of the infection. Pyelitis of infancy persisting longer than the second or third year raises the suspicion that there is some anatomic condition interfering with the outflow of urine.

The involvement of the kidneys may come on with a relapse, usually associated with very violent symptoms, such as hyperpyrexia, convulsions and very soon death. Objectively, the only finding on physical examination is a swelling of the kidneys. In infants the infectious process may produce the gradual diminution of tolerance for food, and death from inanition may ensue, in spite of the best hygienic conditions and feeding.

The relationship of the pyelitis of infancy and childhood to the pyelitis of pregnancy, is still a disputed question. From the lack of evidence of such disturbance in early life, it would seem likely that the two are not related.

Prognosis.—As long as the process is limited to the pelvis of the kidney, the outlook is good, but with the involvement of the kidney, the prognosis becomes dependent on the extent of such involvement. The kidney may be affected primarily, as in the cases described by Thiemich, or the process may be secondary. If it is acute, the child usually dies in a few days from diffuse pyelonephritis; if subacute, the kidney may be filled with multiple abscesses, which gradually destroy its function, and end finally in multiple sacs of pus, making it difficult to find normal kidney parenchyma. In this group of cases the phenolsulphonephthalein excretion, and the blood urea findings give very important clues as to the probable outcome.

If pus in the urine is evidence of a general septic infection, the prognosis, of course, is extremely bad. Involvement of the kidney and malformation of the urinary passages which cannot be relieved surgically make the prognosis bad. The mortality from pyelitis is difficult to determine. In private practice I have seen only one patient with uncomplicated pyelitis die in the acute stage. Göppert gives a mortality of 30 per cent. which seems extremely high.

Diagnosis.—The diagnosis of pyelitis, in practically all instances, is made by examining the urine. The symptoms are so indefinite, and, with the exception of fever, are so often absent that in infancy and childhood the urine should be examined microscopically in all febrile conditions. Pyelitis unquestionably is still often overlooked. On the other hand the emphasis that has been placed on the frequency of

pyelitis, and the ease with which it is overlooked, has led many physicians to make a diagnosis of pyelitis every time they find a few pus cells in a specimen of urine.

The difficulty of obtaining specimens of urine, particularly from female infants, deters many physicians from making the examination. With a test tube and a strip of adhesive plaster the urine may be easily obtained from the boys, and, by using a wide strip of adhesive both front and back, from the girls also. A much more convenient way of obtaining it is with the Spicer urinal (Fig. 159). Having collected a specimen of urine in the usual way, when is one justified in assuming that the infant is suffering from pyelitis? In the normal urine, obtained without special precautions from boys, there are not more than two to three cells to the low power field, and not more than from six to eight cells in the urine of girls, when the uncentrifuged urine is examined. The cell count of the centrifuged urine is of very little value in the diagnosis of pyelocystitis. The frequency of an admixture of pus from the vagina, even when there is no visible discharge, makes it essential to obtain a specimen free from vaginal contamination, or purulent admixture from under a tight foreskin. This can be done by washing the infant carefully before applying the urinal. Even with this precaution, it is at times difficult to know whether an infection exists. Consequently it is always wise never to make a diagnosis of pyelitis which is not based on the finding of bacteria and pus in a catheterized specimen of urine. A great many so-called cases of pyelitis, complicating extra-urinary infections are nothing more than mild vaginitis, such as may occur with a febrile attack. To illustrate: The four year old daughter of a physician had had repeated attacks of acute tonsillitis, complicated each time with a mild pyelocystitis, which yielded readily to alkaline treatment after the subsidence of the tonsillitis. In the attack which I observed, there was severe tonsillitis with fever of 103 degrees. The urine, on this day, was free from albumin and contained only an occasional pus cell. A specimen examined the following day, within an hour after being passed, contained large numbers of pus cells, some in clumps, and innumerable bacteria. There was no visible vaginal discharge. The condition was apparently a repetition of the previous attacks. The second day after the onset of the tonsillitis, the patient passed a small amount of urine in the usual way, and was then catheterized. At this time there was no visible discharge, but a slight redness of the labia where they were in contact. The catheterized

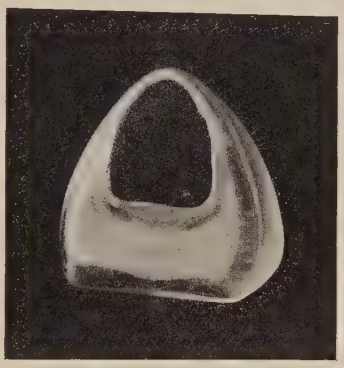

Fig. 159.—Spicer urinal.

specimen did not contain pus, and was sterile on culture, whereas the urine obtained in the usual way, contained pus and bacteria in sufficient amounts to justify a diagnosis of pyelocystitis from this examination alone. The rapidity with which a large number of cases of so-called secondary pyelitis clear up is also in favor of the theory that they are merely cases of mild vaginitis.

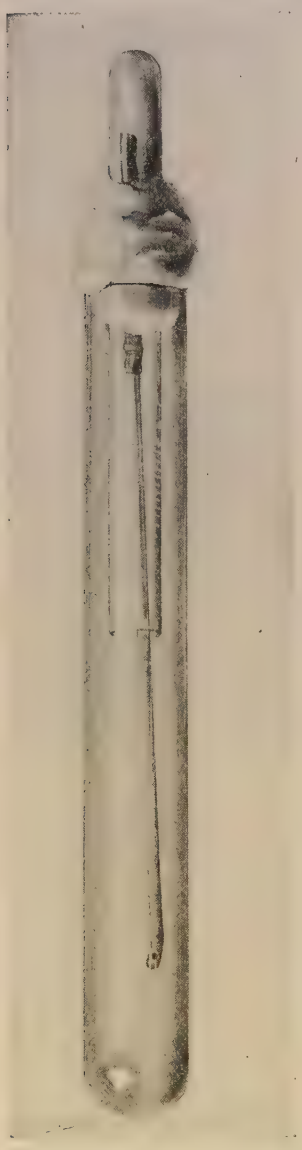

Fig. 160.—Catheterization equipment.

Technique of Catheterization.—The catheterization of the female infant is usually not difficult because the urethra is distinctly visible when the labia minora are spread apart. Occasionally adhesions between the labia minors must be broken up before catheterization can be accomplished. The area around the urethra should be carefully washed with a 1 per cent. solution of lysol, or sterile water. After drying the opening of the urethra with a sterile applicator the catheter may be inserted. In infants less than six months old, the urethral opening is occasionally hidden by a fold of mucous membrane extending forward from the hymen, seemingly to protect the urethra from contamination. In these cases the catheter is passed backward in the midline and usually slips into the urethra, although not infrequently it passes into the vagina. A sterile glass or metal catheter can be carried as shown in Fig. 160, the small tube being used to receive the urine. The small piece of rubber tubing has been found to be of great help in preventing contamination and in controlling the flow of urine. It is always well to let a few cubic centimeters of urine pass before collecting the specimen, as the introduction of the catheter may carry in bacteria from the urethra. In the male infant a large ureteral catheter is used after careful washing of the glans. From urine obtained in this way it is usually possible to make a diagnosis of pyelitis by the presence of pus and bacteria. It is well not to rely on macroscopic examination, however, because the cloudiness may be due to phosphates, or a clear urine may contain innumerable bacteria and an occasional pus cell. In catheterizing an infant for diagnosis, it is always well to

drain the bladder completely, because with the child lying on its back the pus settles to the bottom of the bladder and does not appear except in the last portion of the urine. Ramsey, and others have emphasized the importance of bacillurias associated with high fever and general symptoms. Whenever possible it is advisable to culture the urine, so as to confirm the pyelitis, and identify the infecting organism. Culture should be made in a solid medium, using litmus lactose agar and blood-agar plates. Pus found in a specimen of urine, which proves to be sterile by the usual cultural methods points to an infection with tubercule bacilli. There are exceptions to this, however. Pyelonephritis with large amounts of pus and pus casts in the urine has been observed when the urine was sterile repeatedly, and later only occasional streptococci were found. Certain leptothrix infections give sterile cultures with the customary cultural procedures. Objections to catheterization have been raised because of the danger of infecting the urinary passages. This applies only to the group of cases, in which there is evidence of urethral stricture. In no other type of cases is there any real danger of causing an infection.

The examination of the blood is of value, inasmuch as a moderate leukocytosis is usually present, but does not help materially in a differential diagnosis. Increased blood urea, and enlargement of the kidneys assist in making a differential diagnosis of kidney involvement.

In the acute stage of pyelocystitis the phenolsulphonephthalein output is usually temporarily reduced, as shown by Smith, but rapidly returns to normal after the subsidence of the acute symptoms. It is principally of value in the differentiation of renal involvement.

Treatment.—As pointed out by Hüttenbrenner in 1876, the most important feature in treatment is the washing out of the urinary passages. The process of flushing is limited only by the amount of fluid the child or infant can take. Occasionally infants will refuse to take fluid, or they may be so toxic they cannot take it. It is then advisable to use the stomach tube. In infants it is well to reduce very considerably the food intake, so as to utilize the appetitie in an effort to increase the fluid intake. An attempt should be made to give an infant at least one quart of fluid each 24 hours in addition to its food, and as much more as possible. It is usually found that infants prefer water, either plain or slightly sweetened with saccharine; older children take fluid best in the form of water. A teaspoonful of water given to an infant every 5 to 10 minutes will amount to considerable in 24 hours.

When, because of vomiting, it is impossible to force fluids by mouth, than cay be given by rectum. If given in this way, they are best administered by the interrupted rather than by the continuous method. It is exceptional to find an infant, or even a child under six or seven years who will take fluids well by the Murphy drip. On the other hand, most infants will absorb from 60 to 100 c.c. given high in the sigmoid at intervals of from there to four hours. It is usually advisable to hold the buttocks from 5 to 10 minutes after the adminis-

tration of the enema. In this way from 450 to 750 c.c. of fluid can be given during the 24 hours. A physiologic salt solution can be used, but it is even better to give 7 per cent. glucose to aid in maintaining the nutrition. If alkalies are used, bicarbonate of soda can be given by this route. When it is impossible to give fluids by oral or rectal administration, the intra-peritoneal route in the one preferred. Large amounts of fluid can be given, depending on the size of the child. One hundred cubic centimeters to four hundred cubic centimeters may be given at each injection. The administration is continued until the abdominal wall becomes definitely tense. The absorption is very rapid so that the injection can be repeated at intervals of from six to eight hours. If, because of marked distension, it is deemed dangerous to give the intra-peritoneal injection, physiologic salt solution or 7 per cent. glucose solution may be given subcutaneously or intravenously.

Besides the use of water, the alkaline treatment has given the best results in the acute cases. Alkalies in the form of sodium citrate and sodium bicarbonate are administered until the urine becomes definitely alkaline. In certain severe cases, enormous doses are required to obtain this result. As a routine procedure equal parts of sodium bicarbonate and sodium citrate may be given in 0.65 gm. (10 gr.) doses six times in 24 hours to infants under six months of age. This dose may be doubled each day until the urine becomes definitely alkaline. For infants over six months 1 gm. (15 gr.) is used in the same manner. Usually when alkalinization of the urine is effected the temperature drops to normal, although this is not invariably the rule. Although the temperature returns to normal, the urinary findings remain practically the same. No alkalinity that can be produced in the urine is sufficient to inhibit the growth of the colon bacillus. The most alkaline urine obtainable has a hydrogen-ion-concentration of 8.6, but the colon bacillus does not stop growing until 9.4 is reached. It is probable that whatever beneficial effect the alkali produces, besides its diuretic effect, is by a direct action on the tissues rather than on the bacteria. The alkali treatment definitely hastens symptomatic improvement. The temperature drops to normal, and the child's general condition appears improved. The urine alone remains unchanged. With alkalis alone it may be difficult to overcome the infection. With the alkaline treatment in the pyelitis of older children recovery may not be as rapid as in the pyelitis of infancy.

Next to the alkalies, the urinary antiseptics are of the most value in the treatment of pyelitis. Of these, urotropin and salol are the most commonly employed, the latter particularly in continental Europe. Urotropin seems to give the best results in clearing up the chronic cases. There is no doubt that some individuals have an idiosyncrasy to the drug, so that even small doses may produce hematuria, or vomiting from the effect on the stomach. This factor can be carefully watched, and need not deter the use of the drug. The dose usually given, i.e.,

1 to 2 gr. three to five times a day, is rather low. Since the action is supposed to depend entirely on the formaldehyde, which is dependent on the degree of acidity, the concentration of the urotropin, and the length of time it has to act, we have a set of conditions that must be very carefully controlled. I have been giving urotropin to infants more than six months in doses of 0.65 gm. (10 gr.) four times a day every six hours, and controlling the acidity of the urine so as to keep the hydrogen-ion concentration between six and seven. This can be accomplished by testing the urine for acidity with litmus paper and with methyl red paper for an acidity of less than hydrogen-ion concentration 6. In older children up to 1.5 gm. (22.5 gr.) can be given every six hours, four times in 24 hours, with good results. With such doses, it is advisable to force fluids as much as possible. Although the action of urotropin is supposed to be due entirely to this splitting off of formaldehyde, I have seen a considerable number of chronic infections clear up under urotropin treatment in which formaldehyde could not be found in sufficient concentration to be bactericidal or bacteriostatic in the time urine normally remains in the bladder. Salol can be given in doses of from 0.1 to 0.3 gm. four times a day to infants and up to 0.5 gm. four times a day to older children. We have used 1.0 gm. five times a day with the production of dark urine (indicating the presence of hydrochinon and pyrocatechin) without obtaining antiseptic action.

Local treatment has been effective when applied to the kidney pelvis by ureteral catheterization in chronic cases. It has also been recommended in acute cases with apparent blocking of the ureter, as evidenced by sudden cessation of pus in the urine. Irrigation of the bladder with silver nitrate, or boric acid solution has not produced a cure, in the hands of most observers, although recently Hirst, and Paulson have again advocated its use.

In most instances pyelitis has been uninfluenced by the use of vaccines made from cultures of the patient's urine. Recently Cowie has reported good results with the use of foreign protein in the treatment of pyelitis.

The general treatment consists of rest in bed as long as there is any fever, and for a week to 10 days thereafter in the severe cases. An increase in the amount of pus after the patient gets up is sufficient reason for putting him back in bed. The local tenderness and pain may be treated with local hot applications over the bladder region.

Symptomatic recovery is relatively easy to obtain, but no patient should be considered cured whose urine is not free from pus and bacteria on two successive examinations and cultures.

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TUBERCULOSIS OF THE KIDNEY

Tuberculosis of the kidney is always secondary to a tuberculous focus elsewhere in the body. As a rule, it is merely a part of the generalized process throughout the body. Carried to the kidney in the blood stream, the tubercle bacilli give rise to tubercles scattered throughout the kidney. On comparison with the tubercles in lung, liver, and spleen, they are few in number. In some instances the bacilli may be excreted through the kidney without demonstrable lesions of the organs at necropsy. Tuberculosis of the kidney is rare before the tenth year, and no cases have been reported under five years. Practically all the patients on record are more than 10 years of age. Braasch, in 532 patients who were operated on for tuberculosis of the kidney, found only two (0.4 per cent.) less than 10 years, and 37 (6.7 per cent.) between 11 and 20 years. Wild bolz, in a series of 316 cases reported only four less than 10 years, and Cabot and Crabtree, in 70 cases, found only one less than 14 years. Tuberculosis of the kidney is a relatively unusual condition in spite of the fact that some cases are unquestionably overlooked.

The primary lesion generally is in the cortex from which, by direct extension the medulla, and finally the pelvis, become involved by way of the blood stream. There may be multiple foci in the kidney, so that one pole or the entire organ may break down and caseate. The ureter usually is somewhat involved, as well as the bladder in the more extensive cases. Both of these organs show a great tendency to heal when the infected kidney is removed. The involvement of the bladder is less common in the child than in the adult.

The symptoms are usually indefinite, and may be entirely lacking. Pyuria in a tuberculous individual should always be regarded with suspicion. When culture of the urine is sterile in the ordinary medium, the process is nearly always tuberculous. Even when a complicating acute infection is present tubercle bacilli must always be looked for. Especially in tuberculosis of the bones, the urine should be carefully examined, as renal tuberculosis may coexist without symptoms. In the majority of cases, the primary symptom is pain in the region of the kidney, and if the bladder is involved it is always markedly irritable. Profuse hematuria may be the first symptom.

Report of Case.—Case 2 (A416933), H. E., a boy, aged 14 years and except for measles, mumps, and whooping cough, had otherwise been well until his present illness. Four months previous to admission he had begun to have frequency of urination, micturating every 10 minutes during the day and night. Bladder irrigations gave only slight relief. Two months before admission he had passed blood for the first time. Since then he had passed clots often. He had been losing weight and strength for the last two months.

Examination.—The patient was well developed, and well nourished, but somewhat anemic. The D'Espine sign was positive; the lungs were otherwise negative. There were no tubercle bacilli in the sputum. The von Pirquet test was strongly positive. Urinalysis showed albumin, red blood corpuscles, pus, and tubercle bacilli. The phenolsulphonephthalein output was 45 per cent. in two hours. The blood urea was 30 mg. for each 100 c.c. blood. The cystoscopic examination revealed extensive deforming cystitis. It was impossible to find either ureteral meatus. Exploration of the kidneys was advised.

The left kidney and ureter were found to be normal. The right kidney did not appear greatly enlarged, but there was marked involvement of the upper pole with destruction of about 50 per cent. of the kidney substance. The right ureter was thickened to nearly 1 cm. in diameter. The right kidney was removed. The patient left the hospital after three weeks, completely recovered. According to the latest report from patient he was doing well.

Diagnosis.—The presence of pyuria in a tuberculous patient is presumptive evidence of renal involvement, and if it is associated with enlargement of one kidney, the diagnosis may be definite. Profuse hematuria is usually of tuberculous origin, although simple pyelitis

may begin in the same way. In order to rule out the smegma bacillus, a catheterized specimen of urine should be examined.

Treatment.—General measures are usually of very little help in this condition. The infection is generally unilateral, and when ureteral catheterization shows the other kidney to be normal in function, as evidenced by normal phenolsulphonephthalein output and normal blood urea, the infected kidney should be removed, provided the child is not too seriously ill. Removal of a tuberculous kidney often influences the other lesions beneficially. Surgical intervention is usually not indicated in children, as it is part of a general involvement.

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PERINEPHRITIS; PERINEPHRITIC ABSCESS

Perinephritis is an inflammation of the loose areolar tissue around the kidney, which may terminate in resolution or proceed to suppuration, becoming a perinephritic abscess. The condition may be primary or secondary to infection in the kidney or elsewhere in the body. The primary form is apparently the most common in childhood. All of Gibney's 28 cases were of this type. The exciting cause was trauma, exposure, or some unrecognizable factor. The immediate cause, however, can merely produce an area of lowered resistance; the infection must be conveyed by the blood stream. It has not been decided whether this infection settles primarily in the peripelvic fat, or whether it localizes in the cortex of the kidney, and by rupture extends into the fat. The condition is frequently caused by infection with the *Staphylococcus aureus*, which has a tendency to localize in the cortex of the kidney, and produce multiple abscesses. Rupture of the latter into the peripelvic fat would produce a perinephritic abscess. Baum described seven cases of perinephritic abscess, six of which were caused by staphylococcus infection. Cabot and Crabtree also point out this relationship between the staphylococcus and perinephritis. Without careful control of the urine, it is impossible to determine whether or not there is involvement of the kidney. If the abscess breaks into the perinephritic tissues, it probably will break not into the collecting tubules of the kidney, and thus evidence of infection may never be present in the urine.

Gibney, in three publications, recorded 28 cases of perinephritis which he had observed in the course of the seven years from 1873 to 1880. Townsend, reporting from the same institution, observed only six cases in the nine years from 1894 to 1903. The youngest patient having perinephritic abscess was only five weeks old. The infant

was in constant pain and a high fever. After two weeks of observation, a mass in the loin suddenly developed which, after incision, healed within two months. The literature of the last 15 years is almost barren of contributions on this condition in childhood, and it would almost seem as though it is not so common now as it was 25 or 30 years ago. In Gibney's second paper he reported the histories of three patients who recovered without the formation of an abscess, and of his total of 28 cases, 12 terminated in resolution, and in 16 abscess developed. The abscess usually manifests itself in the ileocostal space, where it is recognized as a definite fullness tender to the touch. Occasionally it points in the hypochondrium, or it may simulate a psoas abscess, pointing in the loin or above Poupart's ligament. It may rupture into the bladder, bowel, or even burrow upward and discharge through a bronchus.

Symptoms.—The onset may be acute with chills, high fever, and general signs of an acute infection, without any definite localizing symptoms; or the onset may be gradual, with subfebrile temperature, stiffness of the spine, a limping gait, and indefinite pains suggestive of a tuberculous process. As a rule, pain is the first symptom, but in young children it is not well localized, and may be referred to the lower abdomen, and in the area of distribution of the peripheral nerves. Pressure on the affected side usually elicits pain. The spine is generally held rigid, and may be flexed laterally toward the affected side. The frequent involvement of the sheath of the psoas gives rise to tension, which is relieved to some extent by drawing up the leg and relaxing the muscle. The thigh is flexed, and to compensate, the pelvis is tilted, and the patient walks on this toe like a patient with a tuberculous hip. Depending on the virulence of the infecting organisms, the constitutional symptoms are mild or severe. In a condition of sepsis with no definite localizing symptoms, a perinephritic abscess should always be looked for.

On walking, pain may be present in the leg of the affected side, with or without deformity, for some time before tumor formation is evident, and may clear up without abscess formation. The abscesses may be of enormous size, as reported by Holt, extending from the spine to the mid-line of the abdomen, and from the crest of the ilium nearly to the free border of the ribs.

Involvement of the lower urinary tract is exceptional; only one of Gibney's cases showed such involvement. Townsend does not mention urinary involvement in any one of his eight cases. Braasch, in a series of 107 cases of perinephritic abscesses, mentions pyelonephritis is only 25 per cent. of the cases. These findings do not exclude a small cortical lesion as an etiologic factor, which might be entirely overlooked in the usual examination. Depending on the severity of the infection and the development of the abscess, the duration of the disease varies from one to six months. Unrecognized cases may persist until there is rupture of the abscess into the peritoneum, bladder,

intestines, or bronchus. Incision and drainage usually result in rapid recovery.

Diagnosis.—The forms of the disease which presents no definite localizing signs and manifests high fever, leukocytosis, and general symptoms of sepsis, is the most difficult to recognize. Pressure on the lumbar region will usually elicit pain. In making a diagnosis a distinction must be made between acute osteomyelitis of the spine of tuberculous or pyogenic origin, and acute tuberculous involvement of the hip joint. In perinephritic abscess there is the acute onset, leukocytosis, high fever, scoliosis rather than kyphosis, and localization of pain while in tuberculosis of the spine there is a gradual onset increasing deformity, tendency to support the trunk, and a positive von Pirquet test. The flexion of the hip in perinephritis is due entirely to tenderness of the psoas, which manifests itself only on extension, when the pain is usually referred to the knee or the hip. Other motions of the hip can be performed without pain. There is a tendency to variation in the degree of involvement. Roentgenograms will also show differences.

When the condition is recognized, the prognosis is good. Draining of the abscess usually leads to rapid recovery. All of the patients discussed by Gibney recovered. Townsend reported eight recoveries in his eight cases. Lente's patient, a five weeks old infant, was ill but two months, recovering rapidly after drainage.

Treatment.—Rest in bed is essential in the treatment of perinephritis and perinephritic abscess. Hot applications to the affected area until there is a definite localization with early drainage so as to prevent possible rupture into internal organs is indicated.

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CHAPTER C

URINARY LITHIASIS

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Lithiasis, or stone formation in the urinary tract, in strict sanity differs in no measure in the infant or child from the same process in the adult organism. Pathologically, it may or may not be of immediate serious portent though it is always pathologic. Clinically, symptomless cases occur in both adult and child. In both may be found the most distressing manifestations of a clinical or pathological nature leading to unmeasurable, dire consequences to the individual through oversight or neglect. Clinically, however, the picture must be retouched, for it is here that differentiation offers encouragement.

The discovery of the condition (especially of renal stone) in an infant or small child provokes much interest and concern owing as well to the tender age of the patient as to the hitherto comparative rarity of it's discovery before death.

Our chief sources of light on this subject are to be sought in the recent reviews, more especially of the French and German. In earlier literature the subject has been treated with reference to older children, including those up to 15 years of age. In some of the modern textbooks, no mention is made of renal stone in infants; in some others the subject is given scant attention. "Stone in the bladder" and "gravel in the urine" occupy places in literature extending many years back, the treatment by medicinal and dietary measures being placed in the foreground. Until recent years—notably since the advent of the *x*-ray —little attention was given to the diagnosis or to the surgical aspect of stone in the infant kidney or ureter, though bladder stones have for generations been treated surgically.

My interest in this subject was first stimulated a few years ago by the following case of renal calculus in an infant which came under my observation and which I reported in 1913.[12]

History.—The infant was a 16 months old male, born in Minnesota of Bohemian parents, neither of whom ever complained of urinary trouble. The mother's brother, a lad of about seven years, had been known to pass gravel with the urine in his early days.

The baby had been circumcised at four weeks of age, was breast fed for the first year and suffered none of the usual children's diseases, with the possible exception of "colics," until the onset of the present trouble. Until several months old, according to a certain custom, the baby was kept wrapped about, arms confined to sides by a long scarf or long quilted band, allowing no exercise of the arms or legs except once daily when the band was removed for a short time.

Examination.—I saw the infant late one December afternoon, 1909. He had not urinated for 24 hours. Examination revealed a spherical stone (Fig. 161, *x*) impacted in the extreme end of the urethra. On the extraction of the obstructing stone the baby passed a large teacup and a half of urine. The stone, weighed later, proved to be ¾ gr. and by analysis was composed of earthy phosphates. Three

FIG. 161.—Showing spherical stone "x," which was removed from child's urethra. The other stones were passed by the child at varying intervals.

months following this onset of trouble the father brought to me several smaller stones which the infant had passed. Radiographic examination was advised to determine if possible the presence of other stones in the urinary tract. After a delay of three months the parents brought the patient for such examination. The result of this examination shows (Fig. 162) two stones in the right kidney, one in the

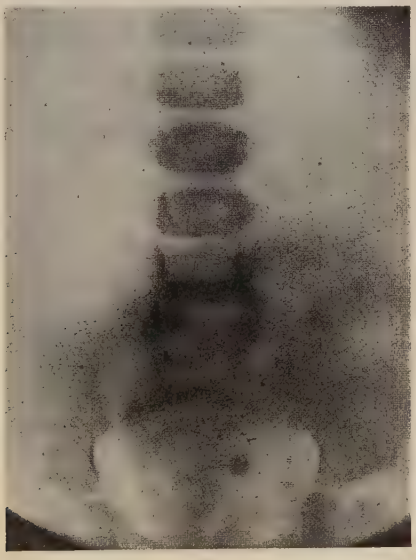

FIG. 162.—Radiograph showing two calculi in right kidney, one in the bladder and a third shadow at the crest of the right ilium—probably stone in the ureter.

bladder, and a third somewhat irregular shadow appearing at about the crest of the right ilium—probably ureteral stone. Radiographs a few days later substantiated the findings at the first sitting. Surgical interference was positively refused by the parents.

Plates taken about nine months after the first radiographs revealed the calculi as before (Fig. 163) but with some destruction of kidney substance. In addition,

shadows in the region of the left kidney appeared, showing the formation of calculi in that organ. The infant continued to pass small calculi at intervals. About a year later the child was operated on in Chicago for bladder stone.

Four years later I received a personal communication from the father to the effect that the child was in fair health, though no relief has been attempted for the kidney stones. The same letter also conveys the information that the child's uncle (the mother's younger brother above referred to in this history) is just recovering from an operation for bladder stone "the size of a pigeon's egg." He was 10 when first operated on, and my letter states that he had passed fine gravel which was first noticed when he was three months old and has done so at intervals since that time. During the last two years his condition has been very much worse.

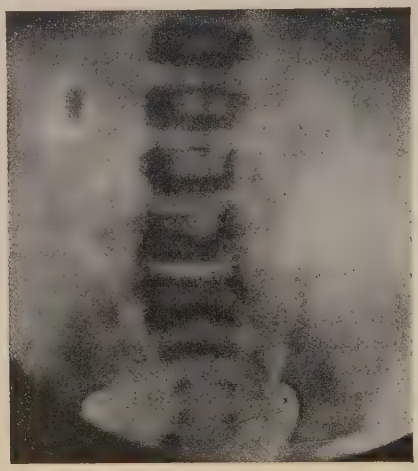

FIG. 163.—Radiograph, taken nine months after that shown in Fig. 162, showing two calculi in right kidney and destruction of kidney substance. Also the bladder stone as in Fig. 162. In addition, two shadows are shown in the left kidney region.

The family history of stone in the above case deserves attention.

As an example of extensive family occurrence it is interesting to note the experience of Clubbe,[27] who operated on the three sons of a fisherman of Lowestoft, England, for stone, at the ages of two, three and eight. The father and mother always had gravel in the urine. The grandfather passed one, and the grandmother passed seven stones. A great uncle was operated on for stone. Six uncles and four aunts all suffered from spells of gravel and, finally, a cousin—an uncle's child—was accustomed to pass gravel.

Too much stress should not be laid on the family tendency, however. Its absence in the clinic history is of little value in ruling out stone in the individual case. In Bokay's[5] wide experience he saw only one case in which he could lay stress on heredity, in the sense of "families of stone formation."

Other cases of stone formation are quoted by various authors, having been found early in infancy, or even before term. Langenbock (Keating's Cyclop. Dis. Child., III, p. 597) found a calculus in the blad-

der of a six months old fetus. Southworth[54] (1895) presented the New York Pathological Society with the kidney of a newborn child containing calculi. Brendel quotes three cases two days after birth. Meigs[36] (Keating, III, p. 596) records the recovery of a calculus post-mortem from the kidney of an infant of six months. Two cases of renal stone discovered in infants of 20 months are recorded by Hance[25] and Partridge[43] (1886). Partridge's case presented no symptoms of calculus during life. The calculus was discovered at autopsy. Jacobson[28] cites a case of a child operated on in which the bladder was found to be in a condition of complete incrustation. At autopsy both kidneys were found to be absolutely filled with stone. G. Newton Pitt[44] (1894) records three cases of renal stone in infants, discovered at autopsy. The first was an infant of 15 months. Death occurred from diphtheria. A kidney stone weighing 4 gr. was found at autopsy. The second was 11 months old when death occurred from diphtheria. The kidney stone in this case weighed 2 gr. The third infant was 21 months old when death occurred from bronchopneumonia. Hematuria had been noticed during life in this case. The stone recovered at autopsy weighed also about 2 gr. Mandhle[72] (1906) records one case, a boy of three and one-half years sent to the hospital cyanosed and delirious—found to be suffering with symptoms of brochopneumonia, with measles as an antecedent. The previous history revealed no definite symptoms pointing to stone. Death occurred suddenly, soon after admission. Autopsy revealed pneumonic consolidation in the lungs. The calices and pelvis of the right kidney were full of calculi, the largest being in the center of the pelvis.

Drew[18] (1905) saw a boy of four years with stone in the bladder for which a cystotomy was done. Four months later a stone impacted in the meatus was removed. The boy's urine then diminished and vomiting began and a calculus was removed from the left kidney and another from the left ureter. Drowsiness increased and only 2½ oz. of the urine passed daily. Death occurred, and at post-mortem a stone was discovered lodged in the lower end of the right ureter.

It is therefore patent to the careful student of this condition that while the past has shed much light on the subject of stone formation, through the advent of death and post-mortem findings, the present marks the threshold to spacious enlargement of methods for its earlier recognition and leading to prompt, definite treatment of a pathologic process hitherto claiming many tender victims.

Occurrence.—Civiale found that 45 per cent. of 5900 cases of calculus occurred in children, and that children under five years are especially prone to the condition. The principle of "survival of the fittest" holds its sway with remarkable tenacity respecting urinary stone. A high percentage of the known cases appear to be those discovered at autopsy. It will be seen by referring to Tables 1 and 2 that of the patients under five years, about 92 per cent. are two years or under and that practically all of these are cases which have

reached the autopsy table. In the past, therefore, it would seem that urinary lithiasis, especially of the renal type, laid claim to a high mortality.

Holt,[81] basing his information on 1000 autopsies, says that small renal calculi are very common in infants, but that they are probably voided during the first years of life because of the fluid diet of the first two years. However possible this may be it is also possible that the fluid diet may in some cases be largely responsible for the condition of urinary lithiasis. As an instance, let me quote Robin's goat-milk case: An infant of 16 months was raised on goat's milk. The infant passed uric acid gravel. Analysis of the milk showed excess of casein. Excess of azote or nitrogenous food was found to be the prevailing diet of the goat. The food of the goat was changed and very promptly the infant's nephritic colics disappeared.

Charvin[9] and several others are inclined to the belief that renal stone in infants and children is a rare condition. Rafin,[46] who collected 39 cases in infants and children, either operated on or revealed at autopsy, says: "The small number of cases attests to the rarity of the surgical form of renal and ureteral calculus during infancy," and he then raises the question as to whether this is a real rarity.

Durand-Fardel and Civiale believene phritic colic in the infant is not a rarity. Gibbons (1896) reports six cases in infants of 9 to 23 months. Bokay[5] (1912) collected in Hungary some 1836 cases of urinary stone in infants and children of ages ranging as high as 15. Of these, 45 were 12 months of age or under, as follows:

Age in Months	Cases
2½	1
3	1
5	3
6	6
8	4
9	4
12	26

The bladder stone cases numbered 1319; one-half the cases were urethral and nine of the cases were of kidney stones. The greater number of cases occurred at three to four years.

The literature is far from being replete with cases of renal stone discovered in infants and treated, whether successfully or unsuccessfully, during life, though recent attention to the subject is tending to bring out more case reports.

From table 1 it will be seen that 98 cases or 91.5 per cent. of the total are two years or under. It will also be found by comparing with Table 2 that practically all of the 91.5 per cent. are post-mortem cases.

How important in the mortality statistics from birth to two or possibly five years is the factor of the stone or stones *per se?* How

TABLE 1.—TO SHOW THE AGE DISTRIBUTION OF CASES OF RENAL CALCULUS IN INFANTS AND CHILDREN FIVE YEARS AND UNDER IN 107 CASES

Name	Under 3 months	3 to 6 months	6 to 12 months	12 to 24 months	2 to 3 years	3 to 4 years	4 to 5 years
Comby	11	17	18	2			
Pitt	0	0	1	2			
Monsseaux	0	0	1	2	3	2	1
Mandble	0	0	0	0	0	1	0
Joseph	12	15	11	2	0	0	0
Drew	0	0	0	0	0	0	1
Nash	0	0	0	0	0	0	1
Southworth	1	0	0	0	0	0	0
Meigs	0	0	1	0	0	0	0
Partridge	0	0	0	1			
Hance	0	0	0	1			
Totals	24	32	32	10	3	3	3

many of the bladder or kidney stones forcing themselves into recognition in later life might be discovered in infancy or childhood? These questions will be taken up as we proceed.

According to Senator[50] it is impossible to make a hard and fast morphologic distinction between renal and vesical calculi. Stones formed in the kidney may soon pass to the ureter or bladder. Carl Beck[3] believes most vesicle stones come from the kidney. Porter's[45] comment is that nephritic calculi are relatively more common very early in life than are vesical calculi.

Certain it is that many of the calculi do not produce morbid phenomena until they reach the bladder. Moreover, there are numerous instances on record to show that definite and very troublesome cases of stone discovered in young adult life had their origin during infancy or childhood. I have called attention above to the relative of my little patient who was operated on about nine years after gravel was first noticed in his urine. The cases quoted by Monsseaux[39] and Charvin[9] which are arranged in Table 3 are illustrative of this fact also.

The endemic, hereditary, dietary and systemic phases in the occurrence of urinary stone are ably reviewed by Hugh Young[62] in Osler's "Modern Medicine" and will not be dwelt on here. It is a significant fact, however, that the children of the poor are more prone to harbor urinary stone than those of the rich. Von Preindlsberger,[59] in reviewing his 271 cases about Bosnion-Herzogovina, claims that lithiasis is far more prevalent in the Christian population than in the Jewish, most likely by reason of the unfavorable conditions essential to living and the bad prevailing diet of the Christian children.

It is an established fact that males are subject to lithiasis more frequently than females. In the statistics given in Table 2 the males outnumber the females two to one. Bokay's[6] statistics show that only 4 per cent. were girls. Coulson's[11] comparison places the figure at 5 per cent. Cunningham[80] found that in a series of 48 cases from the records of the Boston City Hospital, ages 6 to 65, the uric-acid stone occurred in the younger patients, the oldest being 26. Rafin[46] finds urinary stone occurs most frequently on the right side.

While we find here in America no regions where lithiasis is essentially endemic, as in Egypt or in Asia, still the condition is known to be fairly evenly distributed over the different parts of this country.

Table 2.—Showing Recorded Cases, the Relative Ages and Sex Proportion and the Proportion of Autopsy Cases*

Name	Total cases	Cases at autopsy	Under one year	One to five years	Male	Female	Not stated
Rafin	39	28	0	5	24	11	4
Pitt	3	3	3	..	...	..	3
Charvin	45	10	0	..	...	..	?
Jacobson	1	1	0	..	...	..	1
Hance	1	1	1	..	...	..	1
Partridge	1	1	1	..	...	1	
Meigs	1	1	1	..	...	..	1
Langenbeck	1	1	1	..	...	..	1
Brendel	3	3	3	..	...	..	3
Clubbe	2	0	0	2	2		
Southworth	1	1	1	..	...	..	1
Aleksinski	1	0	0	..	1		
Jopson	2	1	0	2	2		
Smythe	4	0	0	4	...	..	4
Sumpter	1	0	0	1	1		
Porter	1	0	0	1	...	1	
Monsseaux	77	?	0	9	51	26	
Comby	48	48	46	2	31	17	
Joseph	40	40	38	2	27	13	
Bokay	45	?	45	..	...	..	45
Mandhle	1	?	0	1	1		
Dun	1	?	0	..	...	..	1
Jaffrey	1	?	0	..	...	1	
Drew	1	?	0	1	...	..	1
Nash	1	?	0	1	...	..	1
Totals	322	139	140	26	140	70	67

* The males outnumber the females two to one. Of the total number of 322 cases, 139, or over 43 per cent., are post-mortem cases.

Etiology.—The etiology of urinary stone has furnished a subject for much discussion. Heretofore, divers theories have been advanced to explain the existence of such calculi. A traditional view holds that the mode of life, diet, and especially nitrogenous diet with wine, beer and little exercise is conducive to stone. Again, any interference with urinary discharge was regarded as a pre-disposing factor. English[27] believed a congenital narrowness of the urethra in the second year to

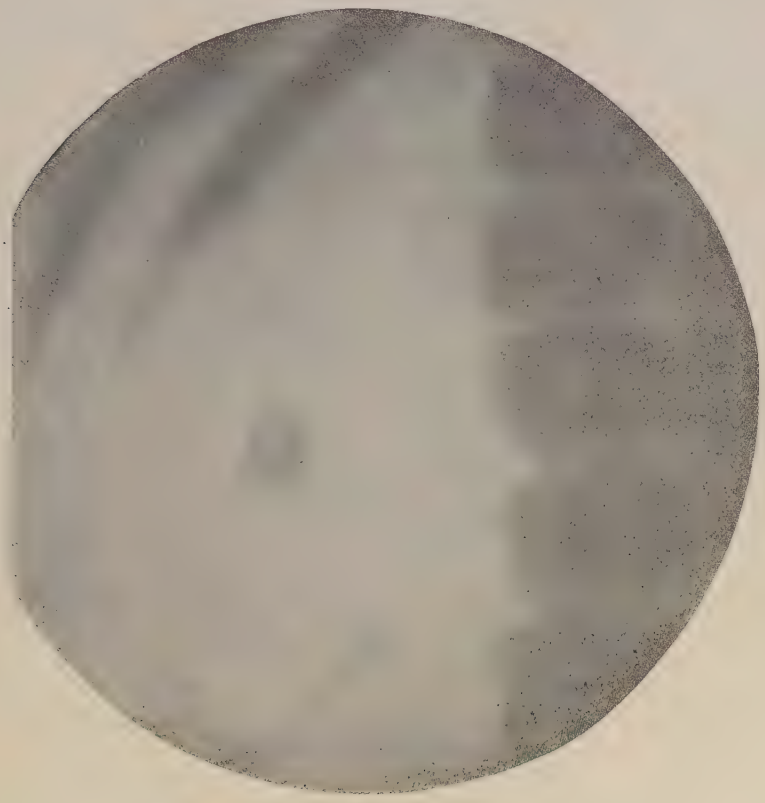

FIG. 164.—Renal calculus, left kidney. (Wm. S. Deutsche.)

be a factor in vesicle calculus in boys. Langstein[31] stated that in addition to uric-acid infarction, endemic conditions have a decided influence on the formation of a calculus; also, that heredity, especially from gouty parents, and still further, the amount of calcium in the drinking water, are important factors. Phosphatic medication was supposed to have an influence in the occurrence of a stone in an infant case reported by Anozan. Comby[66] stated (1897) that the cause of stone formation is poor alimentation and inanition.

The influence of the infectious diseases on urinary litashiis cannot be ignored. M. Nove-Josserand is quoted by Rafin as having recorded

a case of renal stone discovered by the radiograph and recovered at operation in a child who first had a mouth infection followed by bronchopneumonia and later by a grave osteomyelitis. The renal symptoms appeared at the close of the above series of complaints. He quotes, also, Eynard's[22] case, in which the stone was perhaps the result of a grave impetigo. The association of various infectious diseases with urinary stone is also pointed out in connection with Joseph's[30] cases, as seen in Table 4.

A very interesting bit of research might be done by following up a series of exanthemata in infants—especially measles and scarlet fever—looking to the discovery of cases of subsequent urinary lithiasis. Deutsche[16] reported a nephrolithotomy in a 13 year old boy after an eight year history of positive complaint of pain in the left flank. The child was coliky as a baby and had a history of measles and varicella. Urine before operation was 1012; albumen a trace, and a few pus and epithelial cells and red cells. *X*-ray showed a stone clearly (Fig. 164). At operation, a stone the size of a hazelnut was removed and the patient was reported strong and well six months afterward.

Ebert[21] (1912) reports the case of a boy of six with renal colics; chill and vomiting at onset and pains more severe than of ordinary pyelitis. The urine contained red cells and calculus sediment. *X*-ray showed the calculus and operation removed it. The child never had scarlet fever or nephritis but did have measles and whooping cough before the age of three and erythema nodosum at five.

Albarran's classification of renal stones into primary and secondary stone has been widely used and is utilized by Charvin[9] in his study of 45 cases in infants and children. The first form (primary) is considered to be due to or at least associated with gastro-intestinal disorders, deficient alimentation or poor elimination. The second form (secondary) is considered to be due to bacterial activity, chemical modification of urinary constituents and precipitation of urinary salts. The primary is believed to occur in the very young and the secondary in older children, or to put it in another way, the secondary form does not occur in the very young infant.

On this problem of the origin of renal calculi, Schade furnishes an explanation based on certain scientific facts. To quote Robert Milne's[38] summary of Schade's modern work:

"We must comprehend what he means by the terms 'colloids,' 'reversible' and 'adsorption,' as applied to this problem. 'Colloids' are substanes which appear to dissolve in water (*e.g.*, mucin or fibrinogen), but are probably in a condition of suspension, since the osmotic pressure is not affected by their presence. A 'reversible' substance is one which can be redissolved after being deposited from solution, for example, a crystal of magnesium sulphate. Mucin is a reversible colloid. Fibrin is an irreversible colloid. Adsorption is the property colloids have of holding in a solution inorganic substances to an extent greater than could be dissolved in an equal quantity of water. He

would suggest that, for example: Uric acid in urine is held there in its excess by adsorption, on urochrome and other reversible colloids.

"Should the uric acid be in excess of the amount which the colloid can hold by adsorption, we can picture the uric acid being deposited on the colloid. Should the colloid be a reversible one, both colloid and deposits can be removed by more water. If the colloid be irreversible, e.g., if that uric acid be deposited on the surface of fibrin, then no amount of water will redissolve that irreversible colloid—the patient is forming a primary renal calculus which no mineral water or drug ever cured. The colloid is the source of the small amount of matter found in every primary aseptic calculus. The tendency of fibrin to form organic laminæ is the reason for the laminations of these primary renal calculi and, lastly, to cure the patient we have only to diet him in the future to prevent excess of the substances which formed the stone; we have not only to tell him to prevent relative excess by drinking abundance of water, but we have to discover the cause of fibrinuria, or fibrin in the urine, which occurs apart from hemorrhage. This problem has still to be solved."

Joseph[30] describes, in connection with his study of 40 autopsy cases, a peculiar albuminous substance which he found beneath the kidney capsule, morphologically glairy and homogeneous, sometimes occurring in lumps and appearing like fibrin, much the same as the hyaline casts in the urine. He concludes that calculi are caused by renal changes. He observed in kidneys containing stones changes which were the same as those in the opposite kidneys without stones.

Symptomatology.—To await classical symptoms of calculus as encountered in the adult is to waste valuable time. Calculus may exist for a time in the kidney without giving rise to symptoms of any kind. Hewes[26] (1905) maintains however that *any* calculus or crystalline deposit in the kidney, whether the form be gravel or a movable calculus or a fixed stone of either primary or secondary formation, will at some period of its existence cause the appearance in the urine of abnormal features of a nature to suggest its presence.

Beck[3] found that whenever there was a calculus in the bladder he found a renal calculus also. There may be serious paroxysms of pain which are the results of the incarceration of stone. Hematuria is not invariably to be expected, however, when stone is present. Pitt[44] reports a case of stone found at autopsy in an infant of 15 months, in which case no blood had ever appeared on the napkin. The possibility of microscopic blood is to be considered here, however. The history merely states that the infant passed more water than the other babies in the family.

In the observation of Monsseaux,[39] who reports some 77 cases, hematuria was a sign in but eight of the cases. A microscopic examination might reveal more. He mentions a hereditary disposition in 44 of these. According to Durand and Civiale, nephritic colic is not a rarity. Small children are not, however, capable of indicating the

site or the character of the pain. The older the child the less difficulty will usually be found. From the sudden onset of pain the child is apt to cry continuously, and while the pain may at first be in the region of one kidney or the other, later in the attack the pain is usually diffused over the abdomen. Nausea and vomiting may occur with greater or less frequency and present a bilious character. The absence of diarrhea will however be noted to remove suspicion from a possible essential gastro-intestinal disorder. The face is pale and, in the words of Monsseaux, "the expression vividly reflects the pain in the suffering infant." After a few hours the crying and restlessness may cease and more or less small gravel may be found in the urine. Any show of blood should arouse suspicion of urinary stone, or the picture may be presented in which the first alarm is sounded by a cessation of urine flow due to an impacted stone, the finding of which leads to the suspicion of other stones in the urinary tract. Drew's case quoted on a former page shows the importance of suspecting an impacted ureteral stone. The urine should be collected as soon as possible. Blood may be found only on microscopic examination. The tendency to a remission of the symptoms renders the condition very chronic in its course. A radiograph should be taken promptly.

Bladder stone may present some difficulty in urination or impossibility of emptying the bladder; the child cries when urinating and upon occasion the straining in an effort to urinate may cause prolapse of the rectum and occasional stool evacuation. Frequency of urination and eneuresis may be troublesome If the stone is large the pain persists longer after urination. Sudden stopping of the urine may occur. When the child is active, pain may be almost continuous and if the condition is allowed to persist the child voluntarily prefers to remain quiet.

Mention is made of an occasional case in which urinary stone is associated with disturbances of the nervous system. Monsseaux cites one case in which injury to the head at the age of six months was followed by gravel in the urine. Aleksinski's[2] case having "nervous fits" at two years, which will be quoted farther on, has also a suggestion of this nature in it.

Diagnosis.—In many cases of urinary stone in the infant or child a fair sized problem presents. To review some of the case reports or to glance at the foregoing mortality tables suggests this. I have called attention in a previous communication[13] to the insidious process of lithogenesis where pain is not the initial symptom and where the responsibility is placed upon the physician of proceeding along lines which may severely tax his diagnostic acumen. Below the renal tissue urinary stones seem to be found more commonly in the following locations:

1. The kidney pelvis.
2. Junction renal pelvis and ureter.
3. Abdominal portion of the ureter.

4. Pelvic portion of the ureter.
5. Bladder.
6. Urethra:
   (*a*) Fossa navicularis.
   (*b*) Bulbous portion.
   (*c*) Prostatic urethra.

Urine analysis cannot always be relied on to reveal the presence or location of urinary stone, though the urine findings are often suggestive. Microscopic examination of the sediment in a suspected instance may disclose blood or pus cells, or crystals of oxalate, phosphate or of uric acid. The urinalysis, however, presents certain characters in that the urine may be somewhat abundant, the specific gravity 1.023 or even 1.025 or 1.030, the acidity often considerable and a fine precipitate of flakes of uric acid crystals predominating. Microscopic blood and pus cells are usually to be found.

Taylor,[56] quoting from Cabot's statistics, states that in renal calculus cases:

	Per Cent.
The urine was normal in	14
Albumin occurred (varying amounts)	74
Blood	68
Pus	68

Hewes, as stated above, believes any renal calculus will betray itself at some stage by abnormal urinary signs. Ollerenshaw[42] believes the most constant and reliable symptom is hematuria. Transient hematuria may be caused by effect of small grains of uric acid crystals on the tender kidney tubules and is not of much importance. If it persists it must be regarded as serious especially if there be pain along with hemorrhage.

The history of elimination of sand is an important matter to determine if possible; also, the history of frequent or painful micturition should be recognized as suspicious of stone. Hematuria accompanies nephritic colic, especially with oxalic gravel, less frequently in the interval between crises of colic. Hematuria of bladder origin is thought by Monsseaux to be very rare in the infant.

Palpation of the kidney, ureter and bladder regions may not reveal the site of the trouble until late in the attack. If negative at first, it should, therefore, be repeatedly tried. Eliot[20] reports a case in which the kidney was very much hypertrophied, but was misplaced by an accumulation of gravel (presumably in the kidney pelvis). Murphy's "fist percussion" in a modified form may be used over the kidney regions at the back by employing instead of the fist as a plexiimeter fairly vigorous percussion with one or two fingers of the right (or striking) hand. This method may serve to differentiate between involvement of the right or left kidney early in the attack.

Differentiation must at times be made from affections of the liver (rare in infants); also lumbago (rare), Pott's disease and appendicitis.

In a case of Weill's the latter was clearly to be considered in the diagnosis. Nephritis is not rare in the infant. Casts should be searched for. Renal tuberculosis in the infant generally runs an acute course and other organs are involved. Cancer in infants or young children is not accompanied by renal or ureteral pain. Renal tumefaction should be sought and an examination made for symptomatic varicocle, "always pathognomonic to that age," according to Charvin. In infected calculus, pus and very little blood may over-shadow symptoms of its presence. Renal pain is commonly referred by a child to the abdomen, even definitely to the umbilicus. Lumbar pain is uncommon.

Abdominal pain of a spasmodic character accompanied by vomiting, but without diarrhea, dysuria, rapid recovery from the attack and that followed by passing blood and gravel, leaves a tell-tale picture. Hip pain or spine pain may so simulate disease of these regions that the kidneys escape examination. Owing to insensitiveness of the kidney substance a stone here may escape detection. The position and mobility of the stone is therefore quite important in the matter of producing pain. The pelvis and calyces are highly sensitive. Pain is frequently referred to the groin; in boys it is accompanied by retraction of the testicle.

Bladder.—In the diagnosis of stone in the bladder a metal sound may easily be passed in the female, less easily in the male, or a small cystoscope may be used, depending upon the age of the child. Mertz[37] reports having done successive litholapaxies for bladder stone in a girl of five years, in addition to several cystoscopic examinations following litholapaxy.

Rectal examination may be useful in the diagnosis of bladder stone, also of ureteral stone. Faggo and Robinson[46] are each quoted by Rafin as having made diagnosis of calculus in the ureter by this method.

At first the child may cry a little on urinating when no external evidences of irritation are visible. Frequency of urination may play a part here also. As the trouble progresses the bladder pain becomes evident, when the child is active. There is greater pain on urination, leading in some cases to tenesmus and rectal prolapse. Enuresis, accompanied by night crying, occurs; sudden cessation of urine flow may also be a common symptom in some cases (Mertz[37] and Williams).

Ureteral catheterization in the infant is practically impossible. It is difficult to say at what age such instrumental procedures begin to be practicable. Rafin separated the urine in a little girl of six months. Ollerenshaw speaks of cystoscopic examination in one of his cases—a girl of three years.

X-ray.—If the radiograph is important as an agent in diagnosis on the adult, it is of even greater importance in the diagnostic endeavor on the infant owing to the fewer diagnostic measures possible with infants and children. Here it has served to point out many errors which occurred in diagnosis before, and it should be advised in all suspected

cases. Hartman speaks of a case in which a radiograph was not made and the surprise was great at finding stone at autopsy.

Diagnosis should not be considered complete today without a good, clear radiograph. It may not always be complete with the radiograph, but it is certainly not complete without. One who persists in having his suspicious pyuria cases radiographed will sooner or later be rewarded by finding cases of urinary stone. Radiographers believe that a positive plate is more dependable, however, than a negative one, although there is a small degree of error in both negative and positive. In 93 of Leonard's cases five failed to find stones. In 233 of his cases with negative diagnosis a stone was found at operation, or passed, in four. On the other hand, Beneke examined 2400 cases and found no bladder stones. Carl Beck advises radiographing the kidney region in addition to the bladder region when vesical calculus is suspected. It is very desirable that a radiograph be obtained which shows clearly all kidney, ureteral and bladder regions, *i.e.*, the total urinary system. In infants and young children two plates should be sufficient, and usually one large plate will suffice. When two plates are used one should show both kidney and upper ureteral regions; the other should include the bladder and lower ureteral regions. Bladder calculi will be found more often if a systematic radiograph of all cystitis cases is carried out. Kidney stones will be found more frequently if all bladder stone cases are radiographed over the whole urinary region. The necessity of an instantaneous exposure in the case of a crying and wriggling infant needs no elaboration. Immobility of respiration is practically impossible. The dorsal position is found to be the best. The thighs should be flexed, even to the right angle if necessary, in order to eliminate the "saddle-back" and to permit contact of the back with the plate. A purge is advisable before the radiograph is made. The table should be warmed to lessen the trembling. Radiographs of the infant should be very clear reading owing to easy permeability of the rays.

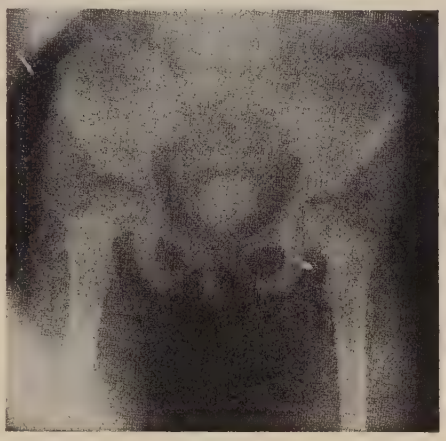

FIG. 165.—Florence B. Referred from Dr. Bowell's service June, 1914. Vesical calculus. (Wertz.)

Urethral Stone.—Impacted stone may be ushered in by bloody urine—the child screaming with pain. Sometimes convulsions occur. The attack may be preceded for a time by difficult urination, or dribbling, or other described symptoms of bladder stone. The child may be nervous or apprehensive.

The knowledge of the localization of stones simultaneously in different parts of the urinary tract is very important. A direct relationship exists between the multiplicity of localization and gravity of operation. Multiplicity of localization also darkens the prognosis.

Prognosis.—Charvin[9] states that lithiasis in the adult may be traced back to infancy. This would lead one to believe that the imme-

TABLE 3.—TO SHOW IN THE CASES OF CHARVIN, MONSSEAUX AND PORTER THE INTERVAL OF TIME BETWEEN FIRST ONSET AND TIME OF ADMISSION; ALSO, WHERE STATED, SIZE OF STONE RECOVERED

Case	Age on admission, years	Age at onset, years	Interval, years	Remarks
Charvin				
4	3½	?	?	Autopsy: Right kidney crammed with small stones. Largest were 12 × 8 mm. (½ × 3/10 in.).
9	10	8	2	Urate calculi.
11	15	14	1	Stone size small pea.
12	12	9	3	
13	6	3	3	Stone weight 8 gm.
16	10	?	.....	¾ × ¼ in.; cylindrical.
17	9	4	5	
18	6	¾	5	
19	11	9	2	Stone 8 × 6 × 4 cm. in size.
20	10	2	8	
21	12	11–12	½	
22	5	4½	½	
29	7	4	3	
32	14	12	2	
35	4	4	0	
37	15	15	0	
39	4	3	1	Stone weight 33 gm.
40	7	?	?	Stone weight 18 gm.
41	11½	1	10	
42	11½	3	8	
43	9	6	3	
Adult cases				
46	16	10	6	Stone weight 25 gm.
47	18	12	6	
48	19	15	4	
49	19	7	12	
50	20	12	8	
51	24	4	20	
52	24	6	18	
53	46	5	41	
Monsseaux				
1	19	5	14	
2	21	12	9	
3	31	10	21	
4	33	15	18	
5	24	12	12	
6	29	7	22	
7	43	8	35	
8	48	13	35	
Porter case				
	4	½	3½	Stone weight 3.9 gm.; size 7/8 × 3/8 in.

diate prognosis is good. Gravel, it is true, is generally of long duration (Table 3). Walther[61] quotes Geraghty that 75 per cent. of stones which enter the ureter are spontaneously expelled. He also observes that 95 per cent. of cases are unilateral.

In Table 3 it will be seen that the interval of time between the date of onset, or at which symptoms pointing to disturbances in the urinary tract occurred, and the date of admission, or such time as patient was presented for treatment, varies within wide limits. In the 38 cases tabulated it will be seen that the interval above mentioned ranged from six months or less up to 41 years, the average being 9.7 years. This is in evidence of the tendency to chronicity with respect to urinary stone. Here we return to the principle of "survival of the fittest." A child well blessed with physical vigor and development will survive the presence of a calculus in his urinary tract longer than one constantly or intermittently ill with intercurrent disease.

Stone in the female bladder if not passed spontaneously may be removed via the urethra depending upon the age of the child. If allowed to remain all the symptoms common to those in the adult may develop. After removal, recurrence is possible so long as infection persists. Litholapaxy offers occasionally a better prognosis in properly selected cases than the more formidable suprapubic operation. Convalescence after this procedure occurs in a brief period of hours, as a rule, and the parents are not so distraught.

Renal operations assume a different aspect. While the infant resistance to this as well as to any operative procedure is small compared to that of the adult yet the urgency of surgical relief warrants it and there are numerous and increasing reports of successfully operated cases. On the other hand, Cabot and Crabtree[8] maintain that the danger of progressive destruction of the kidney if the stone remains is large. H. Joseph[30] has made a very praiseworthy study of 40 cases *post-mortem*, in which stones were found in the kidneys or elsewhere in the urinary tract. None of these were diagnosed during life. Of this material 65 per cent. were bilateral cases. I have arranged some of his statistics in tabular form shown in Table 4 as published in a former article.[12]

It will be seen from Table 4 that diseases of an infectious nature occur in association with calculus and hydronephrosis 70 times out of 107, or 65 per cent. Enteritis and gastro-enteritis are associated with urinary stone and hydronephrosis 19 times; rachitis six times and lobar and bronchopneumonia 20 times.

Diseases of respiratory tract associated with stone or hydronephrosis 29 times.

Diseases of alimentary tract associated with stone or hydronephrosis 25 times.

Systemic diseases associated with stone or hydronephrosis 15 times. Nervous system associated with stone or hydronephrosis 11 times.

TABLE 4.—COMPILED FROM JOSEPH'S 40 AUTOPSY CASES IN INFANTS TWO YEARS OR UNDER, TO SHOW THE RELATIVE FREQUENCY WITH WHICH URINARY STONE AND COMPLICATING HYDRONEPHROSIS ARE ASSOCIATED WITH INTERCURRENT DISEASES IN OTHER REGIONS OF THE BODY

Post-mortem findings	Nephrolithiasis			Hydronephrosis				
	Left kidney	Right kidney	Bilateral	Left	Right	Bilateral	Bladder stone	Totals
Atrophy	1	2	2	1	..	..	..	6
Tracheitis	..	..	1	..	..	..	..	1
Enteritis	2	4	8	2	1	..	..	17
Otitis media	1	1	2	..	..	..	2	6
Gastro-enteritis	..	..	2	..	..	..	..	2
Abscess submax. gland	..	..	1	1	..	..	..	2
Cardiac dilatation	1	1	4	1	..	..	..	7
Bronchitis	1	..	1	1	..	..	..	3
Edema pia mater	..	..	1	..	..	..	..	1
Hyper. mes. lymph-nodes	..	1	3	..	..	1	..	5
Rachitis	..	2	4	..	..	..	..	6
Hemorr. pia mater	..	..	1	..	..	..	..	1
Hydrothorax	..	1	..	..	1	..	..	2
Lobar pneumonia	..	2	5	1	1	..	..	9
Ascites	..	1	..	..	1	..	..	2
Bronchopneumonia	1	2	7	..	..	1	..	11
Meningitis	..	..	2	..	..	..	..	2
Hydrocephalus	..	2	2	1	..	..	..	5
Colitis	..	1	2	1	..	..	..	4
Cystitis	..	..	1	..	..	..	..	1
Abscess mult. cutaneous	..	..	1	..	..	..	..	1
Osteochondritis	..	..	1	..	..	..	..	1
Miliary tuberculosis	..	..	1	..	..	..	..	1
Intestinal tuberculosis	..	..	1	..	..	..	..	1
Pulmonary tuberculosis	1	..	1	..	..	..	1	3
Meningeal hemorrhage	..	1	1	..	..	..	..	2
Diphtheria	..	1	1	..	..	..	..	2
Carbuncle and furunculosis	1	..	1	..	..	..	..	2
Pararectal abscess	..	..	1	..	..	..	..	1
Totals	9	22	58	9	4	2	3	107

Glandular system associated with stone or hydronephrosis seven times.

From this tabulation it also appears that while calculus occurred more often in the right kidney, yet hydronephrosis was more frequent

in the left. Stone and hydronephrosis occurred in the left kidney an equal number of times. In the right kidney stone occurred 22 times and hydronephrosis four times. It would appear therefore that the patient stands an even chance of hydronephrosis if the stone occurs in the left kidney, whereas the patient stands only four chances in 22 (or 2 in 11) of hydronephrosis if the stone occurs in the right kidney.

The evident predominance of bilateral involvement, as shown by Table 4, bears out Rafin and Charvin in that the prognosis becomes more somber with multiplicity of involvement. On 76 observations at autopsy Legeu found 36 (nearly 50 per cent.) cases of bilateral calculi. Kuster, who bases his study on clinical facts, arrives at the proportion of 11.78 per cent. bilateral stones. Leroy[71] found 22 per cent. of bilateral renal or ureteral stones. Of the cases operated on by Rafin he found four bilateral cases, or 8.8 per cent. Bland-Sutton[4] (1916) found that in 10 per cent. of his lithiasis patients stones were present in both kidneys. Watson (1913) has placed bilateral involvement at 30 per cent. but not at the same time. In 19 per cent. stones were present on both sides at the same time.

A highly important lesson to be drawn from the preceding information, therefore, considering the high mortality of cases of multiple involvement, is that the cases must be discovered and treated earlier, before destruction of kidney substance progresses to cripple the organ, or infection becomes a complication. Infection is the *bete noir* of the clinician treating lithiasis patients.

Cuturi[10] (1911) determined from his animal experiments three very potent conclusions: (1) B. coli reaching the healthy kidney by way of the blood stream causes no lesion. It simply causes bacteriuria. (2) B. coli in the kidney complicated by a calculus provokes pyelonephritis and pyonephrosis. (3) Experimentally by separation or ligation of the rectum for 24 hours one obtains a pyelonephritis by the passage of B. coli to the kidney by way of the blood, after ligation of the ureter. If, therefore, the above conclusions apply to the human, an individual harboring a primary stone runs a greater chance of secondary infection when constipation exists.

When the kidney has battled valiantly without surgical relief to rid itself of the demoniacal stone within its vitals and has ceased the struggle, there occurs a complete disappearance of symptoms; but the relief affords a sense of false security, for in the words of Rafin: "Ce silence sera le signe dè la Morte de l'organe"—the silence will be the sign of the death of the organ.

Ureteral stone as well may occasionally take on a serious aspect if it becomes incarcerated. Guisy reports the case of a little girl of 12 in whom a mixed urate and phosphate stone became lodged in the ureter and caused a lumbar abscess, necessitating incision and removal of the stone. Where bilateral involvement occurs the prognosis is brighter where the patient is able to stand operations on both sides at one time. If but one side is treated there is grave danger of anuria,

presumably from reflex inhibition of renal function enhanced by the presence of stone. Gibbon[23] (1913) operated on four cases with bilateral involvement by a unilateral operation. All four developed anuria in 10 to 23 days.

A large number of Monsseaux's patients, many of them older children, were subjects of migraine headache, eczema, epistaxis and conjunctivitis; some were asthmatic, some had urticaria at intervals, others had transient articular manifestations without fever or swelling, but some pain. In his opinion, if the infant is without hereditary taint, the calculus of an accidental sort due to alimentary disorders, poor hygiene, etc., the prognosis is not too severe and the patient's chances are good under better conditions. If, on the contrary, the infant is an inveterate arthritic subject, with bad heredity, is subject to migraines, epistaxis, gastro-intestinal trouble or joint pains, tends to obesity—in a word, is not uremic or arthritic on accasion but by temperament, and is rebellious to treatment and subject to recurrences, the outlook is not so good.

Treatment.—Renal Stone.—We pass from the older literature, which recounts the various methods of dietary and medicinal treatment accompanied by somber high mortality and grave post-mortem intelligence, to the more recent literature. The subject now presents a warmer hue and successful surgical treatment of urinary stone in the infant or child of tender years finds its way into literature.

Unless the calculi are discovered earlier and removed promptly the mortality will remain high. Calculi in the infant kidney or ureter should be expelled or relieved surgically. The destruction of kidney substance, the blocking of a ureter, the danger of infection, are matters for grave consideration when a calculus is the impeding object.

Delay, as suggested by Charvin, enhances the operative risk in that nephrectomy may be necessary in the late stage, where nephrotomy would have sufficed in the early stage. Statistics favor operative relief. Jeanbrau[82] believes the danger of the presence of stone in infants is greater than surgical interference. With the infant or small child the weight of responsibility of removing a diseased kidney rests almost entirely with the operator on account of lack of cystoscopic information in many cases. Examination of both kidneys through lumbar incisions before deciding the operative procedure may thus save an occasional fatality.

An axiom has been stated that "in renal surgery the earlier operation is undertaken after the onset of anuria the better the results." In bilateral cases this axiom finds its largest meaning. In unilateral cases where anuria does not stand out so prominently its meaning is equally important to the side involved on account of kidney destruction.

The risk of operation in the infant or child is somewhat greater than in the adult but the danger of progressive destruction of the kidney if the stone is allowed to remain is large indeed. In 11 operations done

by Rafin on infants and children five were for aseptic stone; six infected. Two had multiple operations. Ten were nephrotomies; three were nephrectomies. A pyelotomy was done in one case. Recovery occurred in all.

The following case histories are given in behalf of surgical treatment:

Ollerenshaw[42] (R): Girl three. Intermittent hematuria several weeks. Similar attack one year before. For three months general health failing. First noticed slight hematuria and tenderness in the back. Albumen present on every urine analysis. No pus or casts. Cystoscopic negative except slight congestion around left ureter. *X*-ray; shadow in left kidney. Stone removed at operation. Small drain. Recovery. Drain out in 48 hours. No hematuria at end of one week.

Nash[40] (W. G.): Boy four. Indefinite history of renal calculus. One definite bit of evidence, i.e, three radiographs each showing distinct shadow region left kidney. Stone removed from renal pelvis. So much bleeding following operation that the kidney was removed. Recovery.

Ebert[21] (O): Girl, six. Ailing two years with "stomach pains." Occasionally dark-red blood in urine. Pain never severe, intermittent, not aggravated by movement, always referred to bladder region. Never vomited. Physical examination: Pale, normal temperature; some pain and tenderness in hypogastrium. No pain or swelling in kidney regions. Blood cells found daily in urine. Relief from pain when kept in bed. *X*-ray; shadow right kidney. Operation three days later, stone in upper pole. Recovery.

Braasch[7] (W. F.) Mayo Clinic: Boy, six. Circumcision at four. Began passing stones in urine at four always accompanied by pain and retention. Sometimes the physician had to push the stones back into the bladder in order that the water might pass. Some of the stones passed the size of half a bean. Last attack three months ago. No blood noticed but pus several times. Health otherwise good. General examination negative. Urine 1014 acid. Albumen a trace, few pus and red cells. *X*-ray: Shadow right ureter, one near kidney and one near bladder. Operation: Removal three stones; one in right kidney, one in pelvis and one in lower ureter. Recovery.

NOTE.—Letter from patient's mother two years following operation; indicates patient free from urinary symptoms but complains gastric distress much of the time.

Braasch[7] (W. F.) Mayo Clinic: Boy 6½. Measles. When two years old had pus in urine; occasionally high colored urine "like blood." Fifteen months ago received a blow right side followed by brief period of soreness. One week ago exploration for abscess right side. Occasionally complaint sideache relieved by lying down for a while. History of sudden acute pain right side and back two weeks ago. Relief by flexing thigh on abdomen. Temperature 100. No nausea or vomiting. Continuous pain in right side and back for two weeks. One week ago on exploration of abdomen a hard mass size goose egg found along ascending colon. Urinates four times daily, five times nightly. On examination whole abdomen tender but soft; mass in right umbilical region like kidney. General appearance of child septic; rapid pulse, coated tongue, herpes on lips. Urine 1010 c.c. (24 hour quantity). Specific gravity 1008 alkaline, albumen a trace, no sugar, occasional pus and red cells. Hemoglobin 52 per cent. White count 16,500. *X*-ray; large stone in right kidney. Operation: Right nephrectomy kidney containing more than a pint of flocculent pus and large stone which completely blocked the ureter; close to the pelvis stone branched and extended down into ureter about an inch. Tumor filled right side of abdomen. Recovery.

NOTE.—Letter from patients father two years following operation. No trouble since operation.

Jaffrey[29] (F): Girl, seven. Suffered two years from frequent attacks of pain in left lumbar region. At operation 11 calcium oxalate stones about the size of peas removed.

Lazelle[33] (H. C.): Boy, seven. For 18 to 24 months attacks abdominal pain passing off in few hours, some attacks accompanied by vomiting. Attacks became more frequent, no relation to diet, worse after activity. Had been called appendicitis. On examination pain referred to umbilicus, slight resistance on right side. Tender posteriorly over right kidney. Urine 1020, albumen slight trace, urates pus and red cells and large hyaline casts and adherent urates. *X*-ray; two shadows in region right kidney. Operation; stones removed. Small drain. Recovery. No signs at end one year.

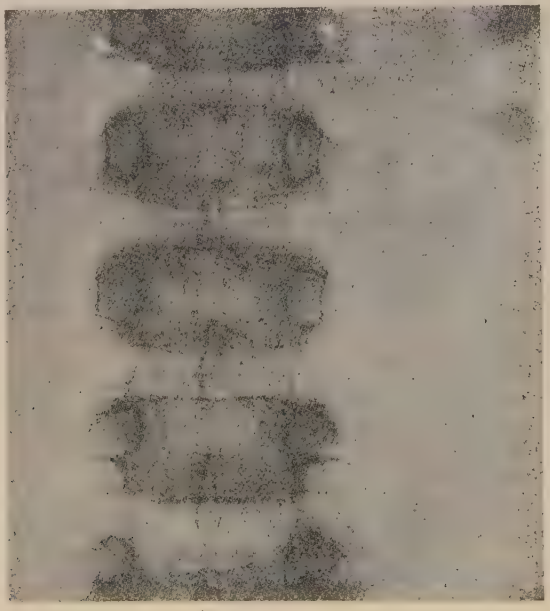

FIG. 166.—Note two stones in upper right hand corner. (Lazelle.)

Ollerenshaw[42] (R): Boy, eight. Suffered occasional attacks left-sided abdominal pain for a year. More severe last three months. Pain aching in character and frequently accompanied by vomiting. On examination nothing abnormal but tenderness left lumbar region and on deep pressure left kidney region in front. Urine; no blood on microscopic examination. Cystoscopic negative. *X*-ray; stone lower kidney region. Operation; stone lower pole. Recovery.

Simpson[55] (G. C. E.): Boy, eight. One month before admission received a blow on abdomen followed by pain at umbilicus for few days. Two weeks later noticed hematuria. Frequency then began. On examination: Weak from loss of blood, no tenderness in kidney regions, phosphatic crystals in urine. *X*-ray; shadows in both kidneys. Operation; 26 stones removed from right kidney. Recovery. three months later operation on left kidney and four stones removed. Recovery.

Braasch[7] (W. F.) Mayo Clinic: Girl, 10. Children's diseases early. Chief complaint—spasm bladder region. Eighteen months ago acute cramp-like pain lower abdomen, bladder region. Pain would last few seconds, one-half to one hour or an entire day with varying severity. Interval irregular—one or two days to three weeks. No pus or blood in urine. On examination fairly well-nourished. Right kidney barely palpable. Urine; 12 hour 160 c.c., 1020 acid, many pus and

few red cells. Hemoglobin 89 per cent. *X*-ray; two stones in right kidney. Cystoscopic showed secretion normal. Operation: Right pelviolithotomy; removal stone from pelvis and stone from calyx pushed into pelvis after dilating opening with finger. Recovery.

NOTE.—Letter from patient one year following operation: "Have not had further trouble."

Braasch[7] (W. F.) Mayo Clinic: Boy, 10. Pneumonia four times. Measles four months ago. *When 13 months old passed eight stones from bladder.* Never passed any since. Complaint; attacks sharp pains over entire lower abdomen. Has been troubled all his life with attacks pain in bladder region so severe as to cause faintness and vomiting, never so severe as to require opiates. Last attack 10 days ago. Attacks generally last 24 hours. Following these he passes pus and blood in urine. Often has fever but no chills. On examination, thin nervous boy. Urine 12 hour 400 c.c., 1016 acid, some albumen, no sugar, large amount pus cells. Combined functional; return in 15 minutes, 130 c.c., 30 per cent. in two hours. *X*-ray; suspicious shadow over lower right ureter and over right kidney. Operation; three stones removed extraperitoneally from right ureter. Second Operation (three months later); one stone removed through incision in right pelvis. Second stone removed from cortical substance. Recovery.

NOTE.—Letter from patient's home doctor five months following operation: "Has gained in weight and is doing very well."

Rodman[48] (J. S.): Boy, 12. Always undersized; otherwise healthy till four years ago when he had cerebrospinal meningitis—nine weeks in bed. Headaches since. Bloody urine at times but no abdominal pain. Never passed gravel. On examination kidneys not palpable or tender. Urine 1020, light-red, albumen slight trace, urates and micro- and macroscopic blood. *X*-ray; stones in both kidneys. Operation; stone removed from right kidney. Recovery. Operation nine months later and stones removed from left kidney. Shock severe and suppression for 48 hours. After cupping, external heat, salt solution and hot packs elimination finally started but he was in desperate condition for one week. Recovery. Left hospital in five weeks in good condition. No headaches.

Braasch[7] (W. F.) Mayo Clinic: Boy, 12. Admitted with fever; pyuria and discharging sinus. Nine months before received 30 caliber bullet wound, bullet entering right side near mid-line between eleventh and twelfth ribs passing through liver and left kidney and removed through skin incision left side. Pus and mucus soon appeared and vesical tenesmus. Seven months ago symptoms acute obstruction with bloating and tenderness. Operation elsewhere revealed sinuses both sides and purulent exudate. On examination one sinus in left lumbar area still persists discharging thick pus and small calcareous particles. Urine 400 c.c., 1015 acid; albumen a trace, occasional pus and red cell. Hemoglobin 65 per cent. White count 7700. *X*-ray; destruction of disc between third and fourth lumbar vertebra. Cystoscopic; right kidney seems normal; left no urine but thick pus in washings. Operation; left intra-capsular nephrectomy; large snail-shaped stone 1 by 3 in. at juncture of pelvis projecting down into ureter; kidney substance practically destroyed; large abscess lower pole. Recovery.

NOTE.—Letter from parents two years following operation: "Has gained in weight and is in splendid health."

Braasch[7] (W. F.) Mayo Clinic: Girl, 13. Appendix removed at six. For five to six months following no trouble, then drawing and dragging sensation in right side chiefly over line of incision. Gradually worse past two years. Tenderness region right ovary, and "sticking pain" region right ovary two or three minutes at a time for past year. No vomiting. Dull ache over right kidney region passing around front to right inguinal fossa. Backache; bearing down in pelvis. On examination; urine 1026. Alkaline, otherwise negative. *X*-ray; stone in pelvis right kidney. Cystoscopic negative. Operation; right nephropelviotomy; stone removed from pelvis. Recovery.

NOTE.—Letter from patient six years following operation: "Dull pain over kidney area good deal of time. Otherwise well."

Ureteral Stone.—In general one may say that while the finding of blood or calculus crystals or both in the urine indicates the *presence* of stone in the urinary tract, the radiograph or the cystoscope or both serve for the localization of the stone. Cumston warns the operator in removing ureteral stone to assure himself of the patency of the rest of the ureteral canal. If on exploration a stenosis is found it must be divided to avoid a subsequent ureteral fistula.

It is well to bear in mind that mobility of the ureteral stone is not exceptional. Escat (1908) while operating in the Trendelenburg position found the calculus 8 cm. distant from the location shown in the radiograph.

In addition to the combined ureterorenal cases quoted above the following case reports of ureteral stone are of interest:

Eynard and Rafin:[22] Girl 6½. Well up to one year, then a severe impetigo lasting two or three months. Bloody urine for nine months. Urine 600 to 700 c.c. in 24 hours. No kidney pain. *X*-ray; right ureter negative; lower left ureter five

Fig. 167.—Multiple calculi in pelvis of ureter. (Eynard and Rafin.)

Fig. 168.—Calculus extracted from the ureter and calyx (life-size). [Eynard and Rafin.]

triangular shadows each 1 cm. An attack of left nephritic colic and bloody urine prompted immediate operation. Transvesical extraction was tried by one of the authors without success. Later ureterotomy was attempted and after considerable trouble the stones were located and removed. The permeability of the canal was demonstrated and a drain left down to the suture line in the ureter. Recovery.

Cumston (C. G.): Boy, 8. Right, sided pain which had been diagnosed appendicitis. Urine showed microscopic blood and leukocytes. Temperature normal. *X*-ray, stone in pelvic portion of ureter size of a date seed. Operations ureterotomy and removal of stone. Recovery.

Vesical Stone.—It is not surprising that bladder-stone cases are more commonly observed. The bladder is in a certain sense a container at the bottom of the urinary system. Into it sand and gravel

are urged partly by gravity, partly by the current of urine through the ureters. Urine which passes quickly through the ureters remains much longer in the bladder. Infected urine thus remaining in the bladder when aided by a traumatizing stone has every opportunity to cause serious disturbance. Thus after removing a vesical calculus strict attention should be given to the clearing up of cystitis in order to avoid recurrence of stone formation. In older children, especially girls, litholapaxy may be chosen for the removal of the stone. Ransohoff (Keen's Surgery) states that where the bladder capacity equals 75 c.c. this method may be applied. Many operators prefer the suprapubic route.

Sumpter[53] reports a case of bladder calculus in a boy baby 22 months old, removed suprapubically with good results and no recurrence. Porter[45] reports the case of a baby girl first seen at the age of six months. She had had colic for two years or more, passing fully a drachm of calculi of small size. Operation was done at 3 years 10 months, and a 60 gm. calculus recovered suprapubically. Good recovery followed.

The very instructive case recorded by Aleksinski[2] is worthy of citation here:

The boy was first seen at seven years, his complaint being painful micturition. At two he had "nervous fits" which were never accurately diagnosed; at five pleurisy with effusion; at six he began to have painful micturition, a thin stream and frequently interrupted. The urine contained pus and blood. The temperature ran as high as 104°F. A diagnosis of vesical calculus was followed by suprapubic removal of the stone. A month later his old symptoms reappeared. Urine 1007, daily quantity 1500 c.c., acid, turbid, pus and blood cells, oxalates and mucus. Albumin present. Bacteriologic examination showed B. coli. Radiograph showed shadows in both kidney regions. Nephrectomy on the right side brought forth three stones the size of walnuts. The urine presented no improvement and three weeks afterward at operation the left kidney yielded four stones. Following this last operation he sat up on the eighth day and was discharged on the seventeenth day. Seven months afterward he was well and the urine was normal.

As in the case just cited, where extensive involvement exists it is an accredited procedure to operate in successive stages. Attention to the bladder stones with neglect of the kidney condition is a grave injustice to the patient. Small kidney stones may pass unnoticed or may lodge in the ureter enroute. Attempts at dislodgment with the cystoscope and ureteral catheter becomes proportionally more difficult the younger the child.

Loùmeaù[35] (E): Girl, two. Frequent micturition daytime at age seven months, pain following. Bladder stone removed which upon analysis showed cystine formation.

Dunn[19] (W. E. N.) Case I: Boy, two and one-half. Dribbling urine and passing blood. No diagnosis by passing sound. Suprapubic cystotomy; whole bladder

filled with a smooth stone so large it was removed by fragmentation. Total operation time two and three-fourths hours. Restless and feverish for 48 hours, subsequent recovery uneventful.

Case II: Boy, three. Patient in agony on account of rough mulberry stone. He neither ate not slept much on account of constant pain. When presented he was almost a skeleton. This stone also fragmented in order to remove it. Recovery uneventful with rapid gain in weight and strength.

In both of Dunn's cases the bladder wounds were left open without tube. Irrigations done twice daily with warm boracic solution. Urine passed in both cases about the tenth day.

Braasch[7] (W. F.) Mayo Clinic: Boy, four. No history of previous diseases. Not doing well past year and attacks every three weeks, frequency and extreme bladder irritation; pain and tenesmus; some blood in urine. Four months ago passed gravel. Never pain in back. Never very strong and probably had symptoms long before recognized. Incontinence. Findings: Patient rather thin. Urine 300 c.c., 1006 acid, albumen a trace, no sugar, few hyaline casts, few pus and red cells. *X*-ray; shadow bladder region size about 1 in. in diameter and another size of a pea in left kidney. Operation: One large bladder stone removed. Subsequent examination: Bladder symptoms much improved, urine clear, gained 5 lb. in weight. *X*-ray; shadow ½ by ¾ in. at ureteropelvic juncture. Operation three and one-half months after first operation): One stone removed from pelvis left kidney. Recovery.

Note.—Letter from patient's mother three years following operation: "No trouble of any kind since operation."

Mert[37] (H. O.): Girl, five. Well till measles at three, ill 10 days, at no time in bed. At age three years two months cried on urinating and then back at play; frequency began and grew worse; severe pain a month later and in two months more on movement. Later difficulty or impossibility of emptying bladder; straining with some prolapse of rectum. Eneuresis. *X*-ray; bladder stone 1½ in. in diameter. Litholapaxy and 10 gm. crushed stone removed. About five weeks later litholapaxy repeated. Cystoscopic examination four or five times following—no stones.

Rendu[47] (A): Girl, eight. Admitted with retention 24 hours. Previously frequent urination. *X*-ray; bladder stone 3.75 by 3.5 cm. Suprapubic cystotomy; removal of stone weight 40 gm., drainage.

Urethral Stone.—As suggested on a former page the attention of the clinician may be first arrested by retention of urine and the finding of an impacted urethral stone. An internal rather than an external urethrotomy should be done where the size of the stone will permit. A suprapubic cystotomy in posterior urethral cases is regarded as better still.

Lehnerdt:[34] Boy one year seven months. Cystitis for one year. Rachitis and a chronic lung infection. Pus in urine. Stone found in urethra, removed; symptoms disappeared at once.

Williamson[60] (T. V.): Boy, three. Sudden stopping of urinary flow in middle of the act. Cried out with pain localized in perineum. Repeated efforts failed to dislodge the stone and pain more severe each effort. Had retention all day. Examination showed stone in bulbous urethra—hard, round, smooth. Urethrotomy: Phosphatic calculus impacted in tissue by force of urinary stream and considerable damage to urethra. Drain removed fourth day. Sent home seventh day. Wound closed in few weeks and no sign stricture at time of report.

Lawrence[32] (C. S.): Boy, five. History three years pain in abdomen and at times bloody urine. Pain paroxysmal frequently bringing on convulsions. For past six months difficult urination, the urine passing drop by drop. Very nervous and every few minutes screamed with pain. Urine contained pus and on examina-

tion a stone size quail's egg felt in membranous urethra. External urethrotomy and removal of stone.

Sampter[53] (W. D.): Boy, seven. Colic from birth and since four months of age under successive medical attention. Had never passed urine in a stream but dribbled small quantities day and night. Always with fretting or sometimes agonizing crying. Never slept without waking several times during night. Examination; stone in prostatic region. Urinary antiseptics given for two weeks then two stones removed by incising the urethra. Complete relief at time of report.

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CHAPTER CI

TUBERCULOSIS OF THE KIDNEY, SYPHILIS OF THE KIDNEY, AMYLOID KIDNEY, PARASITES OF THE KIDNEY, INJURIES OF THE KIDNEY, MALFORMATIONS OF THE KIDNEY AND URETER, CONGENITAL CYSTIC KIDNEY, TUMORS OF THE KIDNEY

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TUBERCULOSIS OF THE KIDNEY

Frequency.—Involvement of the kidneys by tuberculosis is found at autopsy more frequently in children than in adults. In statistics collected by Vignard and Thévenot, renal involvement was present 82 times in 400 autopsies on tuberculous children as compared with 17 times in 300 autopsies on tuberculous adults. This greater frequency is the result of more widespread distribution in the generalized tuberculosis of childhood and the renal tuberculosis is only part of the generalized miliary form of the disease. This type of renal tuberculosis, which has been termed the acute or medical form, is of relatively slight clinical importance as compared with so-called surgical chronic renal tuberculosis, in which the kidney clinically is the organ chiefly or alone involved. This latter form appears to be more rare in children than in adults. Adults greatly outnumber children among the cases of renal tuberculosis that surgeon and pathologist see in hospital work. Of 136 cases of renal tuberculosis operated upon by v. Illyés, 19 were between the ages of 10 and 20 years and none apparently below the younger age. Vignard and Thévenot were able to collect 47 cases of surgical renal tuberculosis in children. The age incidence in this group of cases, where the age was stated, was as follows: Up to 3 years of age, 4; 3 to 6 years, 8; 6 to 11 years, 9; 11 to 16 years, 17. Cautley has reported a case in an infant of 12 months and cases at 3 and 7 months are on record. Oraison ascribed the relative infrequency to failure to make the diagnosis in childhood. The gradually increasing incidence with increasing age in childhood indicates, however, an actual lesser frequency during the earlier years of life. In the Vignard and Thévenot statistics, 21 cases were in boys and 15 in girls, about the same preponderance of males over females which holds for adults. The right kidney was slightly more frequently involved than the left, the proportion being 16 : 13.

Pathology.—In the great majority of cases of chronic renal tuberculosis the affection is unilateral in the beginning. In unoperated

cases the second kidney may ultimately become involved. Several gross pathologic forms are described. Tuffier recognized four types, which do not always show a sharp distinction: (1) Nodose, with or without cold abscesses; (2) tuberculous pyelonephritis; (3) the massive degenerative form; (4) tuberculous hydronephrosis. Albarran made three main divisions: (1) Nodose; (2) cavernous; (3) tuberculosis with dilatation of the pelvis, subdivided into tuberculous hydronephrosis and tuberculous pyonephrosis. Pousson made six divisions: (1) The infiltrative nodose form; (2) the massive degenerative form; (3) cavernous tuberculosis; (4) tuberculous abscesses; (5) tuberculous pyonephritis (usually associated with mixed infection); (6) tuberculous hydronephrosis. These various types are in part evidence of the variation which the chronic tuberculous process may show in any tissue, and in part they are the result of secondary changes which occur in the particular organ involved, namely, the kidney. The degree of dissemination depends in part upon the rapidity of the process. Whether there will be simply widespread caseation or caseation with cavity formation (renal phthisis) will depend upon whether the lesion opens into the pelvis and discharges its material by way of the ureter. If the ureter is occluded, which, according to Verriolis, occurs relatively late and in about 16 per cent. of cases, there may be hydronephrosis if secreting tissue is still present, pyonephrosis if the liquefied caseous material is emptied into the pelvis; or the entire kidney may be transformed into a closed, walled off, caseous sac (pyonephrosis tuberculosa occlusa, Smirnow; tuberculous autonephrectomy).

German and other writers have recognized the same main types described by the above French authors, but Israel added as a distinct form tuberculous ulceration of the papillæ, cases of which have since been described by Widlbolz, Hartmann and others. Oppel (quoted by Smirnow) considers this last form the earliest lesion. His classification based upon what he holds to be the sequence of stages, is as follows: (1) Nephritis tuberculosa pyramidalis (ulcerative tuberculous papillitis); (2) tuberculosis renis cavernosa (cavernous tuberculosis); (3) pyonephrosis seu hydronephrosis tuberculosa (tuberculous pyonephrosis or hydronephrosis); (4) atrophia renis tuberculosa (terminal atrophic tuberculosis). In children the cavernous form is that most frequently encountered at operation. Vignard and Thévenot described two very rare varieties in children, a unilateral miliary renal tuberculosis, and a bilateral tuberculosis of the kidneys and ureters with involvement of the bladder, prostate and seminal vesicles. Calcification may occur in old lesions. From the kidney the process may spread to the surrounding tissues. The resulting perinephritis may be either dense, fibrous and indurative, or caseous and fluctuant.

Since the lesion, at the time that it comes under direct observation, is usually advanced far beyond the stage of miliary or conglomerate tubercle formation which must have been the initial stage, caseation necrosis predominates in the microscopic picture. If the process has

not advanced to the stage of complete destruction of the kidney and if it is still progressive, the caseous area is surrounded by inflammatory granulation tissue in which tubercles are scattered. The degree of fibrosis and of lymphocytic infiltration present in the peripheral diffuse inflammatory zone depend upon the age and the progress of the process.

Except in rare cases where ascending infection is probable, the ureter and pelvis are involved secondarily to the kidney. The ureteral lesions may develop first at its upper end at the ureteropelvic junction, or at the lower, vesical end. The wall becomes thickened by diffuse inflammation and the lumen may be obliterated. Miliary tubercles may be present in the bladder mucosa at the mouth of the ureter and these may go on to ulceration.

Bacteriology.—Renal tuberculosis is the result of localization of tubercle bacilli in the kidney. In view of the relatively high incidence of bovine tubercle bacillus infection in childhood, one would expect the same proportional relations to hold for renal infection. This point has not been sufficiently investigated, however, to permit any definite statement. Griffith's comprehensive tabulation of 1068 cases of tuberculosis in which the type of organism was determined by identical methods under the auspices of the British Royal Commission on Tuberculosis, with a total incidence of the bovine bacillus in 20.7 per cent. of cases, includes only 17 cases of genito-urinary tuberculosis, of which 17.65 per cent. were due to the bovine bacillus. Of this number only two were between the ages of 10 and 16 years and both yielded the human type of organism. The remaining 15 cases were over 16 years of age; of these, three or 20 per cent. were due to the bovine bacillus. In the majority of cases the tubercle bacillus alone is present. If the ureter remains open secondary infection by B. coli or other bacteria may occur.

Pathogenesis.—The infection may reach the kidney by direct continuity from a contiguous focus (tuberculosis of the spine); by transport through the lymph vessels from foci in the abdominal cavity; through the ureter from a lesion in the lower genito-urinary tract (ascending tuberculosis); by the blood stream (descending tuberculosis). The first named possibility is rare. Lymphogenous infection is extremely doubtful. Whether ascending infection is possible or ever actually occurs has led to considerable argument and to some experimental investigation. In a very small proportion of cases the anatomical evidence, namely, advanced tuberculous cystitis with slight renal involvement, favors the belief that the infection has reached the kidney from the bladder. Buerger has recently reported two such cases in adults and presents them as proof of ascending infection, while admitting the infrequency of the process. The experimental evidence is likewise unsatisfactory. Positive results have usually required accessory manipulations of a kind which do not have a counterpart in the spontaneous human disease. The experiments of Wildbolz are the most suggestive, but even he found it necessary to obstruct the

urinary outflow from the bladder in order to cause a backflow of urine into the ureter. With progressive thickening of the ureter from below it is possible that an upward flow of infected urine might occur under natural conditions. Ascending infection by way of the lymphatics of the outer portion of the wall of the ureter, which Eisendrath and Schultz and later Helmholz showed to be possible with B. coli and other common bacteria, apparently does not hold for ascending tuberculosis because of the marked interstitial changes which characterize the process. Wildbolz was not able to bring about ascending infection by inoculation into the outer portion of the ureter wall. A small amount of anatomic and experimental evidence, therefore, favors the view that the kidney may become involved secondarily to a lower lying focus, but indicates also the rarity of this process.

In the great majority of cases the bacilli reach the kidney by the blood stream. In rare instances this may occur when there is no other detectable focus. In the majority of cases the bacilli have been derived from a primary focus elsewhere in the body, in children the lungs or tracheobronchial lymph-nodes, the cervical lymph-nodes, or bone. Often the primary focus is quiescent, or not recognizable clinically because it is overshadowed by the renal lesion. The number of bacilli which enter the blood stream to be deposited elsewhere must be small. In so far as localization in the kidneys is concerned, this is usually unilateral in the beginning. The early stage of the lesion is rarely seen. In the acute miliary form the tubercles are usually widely scattered throughout the renal substance, being especially numerous in the cortex. In the chronic surgical form the lesion often appears to begin at one or a few localized points at the corticomedullary junction. The further changes are like those in a slowly progressing tuberculosis in any solid organ and lead to the formation of a caseous center of varying size surrounded by a zone of diffuse tuberculous inflammation with miliary and conglomerate tubercles in the surrounding tissue. With a breaking of the lesion into the pelvis the infective material may be discharged, with secondary involvement of the pelvis, ureter or bladder. Interstitial inflammation of the ureter may lead to occlusion of the lumen with disappearance of the urinary symptoms, a condition to which the term autonephrectomy has been applied. In a slowly progressive lesion there may be marked calcification.

While the lesion, as one usually sees it, points to an origin from a deeply embedded focus, the earliest lesions which have come to operation have been those of one or more papillæ, ulcerative tuberculous papillitis, as in Schneider's case in a 14 year old boy. It is probably just because of the superficial localization and early ulceration of this process that the diagnosis has been made early in such cases. In this type of lesion it is possible that the bacilli have reached the kidney by the blood stream, but have been excreted into the urine without localization at the point of transit from blood to urine, and have then

become secondarily localized along the course or at the end of the collecting tubules. In the pathogenesis and the later development of the process one would differentiate then between localization from the blood stream in the deeper portion of the kidney substance and localization from the urine stream in the superficial portion of a papilla. In the former the diagnosis will be made late, in the latter relatively early.

Symptoms.—General symptoms, such as loss of weight or a tendency to fatigue easily, may be present even before any localizing signs are noted. These may be due, in part at least, to the primary focus. Early local symptoms relate more often to the bladder than to the kidney, even in the absence of actual bladder involvement. Such symptoms have been considered reflex in origin. Increased frequency of micturition, pollakiuria, especially at night, may be the earliest manifestation. Urgency of micturition, or even incontinence, the latter most often nocturnal and emphasized as a symptom by Constantinesco, may occur early. Urination may be associated with pain referred to the bladder. Hematuria may be a striking symptom, but occurred early in only two of Wildbolz' series of 300 cases. When the blood is small in amount it appears at the end of urination. Legueu and Papin have reported three cases, the youngest in a male of 18 years, in whom the sudden appearance of a large amount of blood in the urine and its continuance for several days was the first thing to attract the attention of the patients. In Alberran's discussion upon this report he said that he had been accustomed to consider such copious hemorrhages as due to an associated hemorrhagic nephritis; but two of Legueu and Papin's cases showed definite tuberculous arteritis as the cause of the hemorrhage. Schoemaker has reported a case in which the first symptom was marked hematuria from the right ureter. Tubercle bacilli were not found. At operation a fluctuant cyst was resected from the convex border of the right kidney. The subsequent microscopic examination proved the cyst to be tuberculous in nature. Several months after the operation tubercle bacilli appeared in the urine. The right kidney, after removal, was found to contain several small tuberculous foci and one large one at the lower pole. Pain in the renal region may be an early symptom. Palpable tumor in this region occurs late. Rafin analyzed the early symptoms in 160 cases of renal tuberculosis, in which the diagnosis was established by operation, with the following results: In 61.87 per cent. the first symptoms were bladder symptoms and in 19.37 per cent. renal; early hematuria, 5 per cent.; cloudy urine, 2.5 per cent.; albuminuria, 1.87 per cent.; renal pain and hematuria, 1 case or 0.62 per cent.; bladder pain and hematuria, 1.87 per cent.; general symptoms, 2.5 per cent.; indefinite symptomatology, 4.37 per cent. In children Vignard and Thévenot emphasize nocturnal incontinence as an early and important symptom. The slight early hematuria may disappear after rest. There may be fever and lumbar pain, especially on pressure. In rare cases palpable

tumor may be the first symptom. Of three cases reported by Marion, in girls aged respectively 15, 7 and 13 years, the first began with lumbar pain and pollakiuria of clear urine, the latter symptom considered highly important; the second began with nocturnal incontinence, which leads the writer to say that this symptom in children should receive more attention than is paid to it; the third case began with frequent micturition, cloudy urine, terminal hematuria, and pain after micturition. In one of Wildbolz' cases, a young girl, lancinating renal pain and polyuria with traces of albumin were present for a year and a half before a definite diagnosis became possible. In general, it may be said that the symptoms of renal tuberculosis in children are much the same as in adults. Urinary frequency and incontinence are important. Since such urinary disturbances are frequent in children, the tendency to consider them of little moment must be guarded against and the possibility of renal tuberculosis should be borne in mind.

Diagnosis.—The diagnosis rests upon careful consideration and evaluation of the general and local symptoms, upon thorough examination of the urine, upon Roentgen-ray examination, and upon cystoscopic and ureteral examination when possible. The symptomatology has been sufficiently considered above.

Urine.—The total 24 hour quantity may be increased in the early stages and the urine may be clear at this stage. Bazy lays stress upon a "loss of brilliance," which occurs without a loss of transparency or gross clouding. The acidity of the urine may be increased. Albumin is usually present; it was absent in only 7 of 166 of Rovsing's cases. These earlier and slight urinary changes may be the result of reactions in the secretory tissue about the lesion of the involved kidney or of compensatory changes in the other kidney. At a later stage the urine becomes cloudy through the presence of cells. The latter are chiefly polymorphonuclear leukocytes; lymphocytes do not predominate in the urine as they do in the lesion itself. Micheli considers the leukocytic degeneration of Columbino specific and of even greater value than the search for bacilli. In the freshly voided urine the leukocytes vary greatly in shape; their contour is irregular, with small protoplasmic buds which may be detached. Doubt must be expressed as to the specific nature of these leukocytic changes. Wynne considers leukocytic degeneration suggestive but not pathognomonic; absence of the degeneration does not eliminate tuberculosis. Red blood corpuscles may be present, in small numbers in the hematuria which may occur at the end of micturition, in larger amounts in the rarer cases in which large blood-vessels are opened by the specific inflammatory process.

Bacteriology of the Urine.—The finding of tubercle bacilli in the urine is the most important diagnostic aid. Wildbolz claims 70 to 80 per cent. of positive results in advanced cases; in early cases the bacilli will be found in a smaller percentage. Gautier claims 80 per cent. of positive findings with careful technique. The latter must differ-

entiate between other acid fast bacteria which may occur in the urine, as the smegma bacillus, on the one hand, and the tubercle bacillus, on the other. The latter organism retains the carbol-fuchsin stain after treatment with both acid and alcohol, whereas the smegma bacillus is only acid fast. The chances for finding the bacilli are increased by using the entire 24 hour specimen of urine. This should be allowed to sediment spontaneously for 24 hours under toluol, preferably in a large conical glass. The lowermost portion of the fluid is then withdrawn by means of a pipette and subjected to prolonged, rapid centrifugation. Kolischer and Katz believe that the subcutaneous injection of tuberculin increases the number of pus cells and of bacilli in the urine and is an aid in diagnosis. The various methods for the examination of the urine for tubercle bacilli have been reviewed by Watson.

Question has been raised as to whether the presence of tubercle bacilli in the urine is sufficient of itself to warrant an absolute diagnosis of renal tuberculosis. It has been claimed that bacilli may appear in the urine without definite involvement of the kidney when there is a tuberculous process elsewhere in the body, and that slight albuminuria may be associated with the bacilluria even in the absence of actual renal tuberculosis. Kiellentheur, therefore, says that for the diagnosis of surgical renal tuberculosis there is necessary the triad of bacilli, leukocytes and red blood corpuscles. Wildbolz maintains the same position. Bernstein has investigated the occurrence of tubercle bacilli in the urine in the absence of renal tuberculosis. By inoculating guinea pigs with the urine from a series of 100 patients with pulmonary tuberculosis he obtained 10 per cent. of positive results; there was no clinical evidence of renal or urogenital tuberculosis in these cases. Autopsy on 320 cases of pulmonary tuberculosis gave 3.4 per cent. with renal tuberculosis. Opposed to the above are the findings of Spitzer, Williams, Burdick and Craney, who conclude that the normal epithelium of the genito-urinary tract does not excrete tubercle bacilli and that when bacilli are present in the urine there must exist a tuberculous lesion in the tract. They found tubercle bacilli in the urine of four of 100 cases of pulmonary tuberculosis; of these four cases, three were proven to have lesions in the genito-urinary tract. Perhaps the safest conclusion is that the value of the presence of tubercle bacilli in the urine is a relative one, which should be supported by other urinary findings or symptoms.

Animal inoculation: In suspected cases, if bacilli are not found in the urine, or if there is doubt as to the nature of acid-fast bacteria which have been found, the sediment from the centrifugated urine should be injected into guinea pigs. If the material is injected subcutaneously, the inguinal nodes will usually be first involved; at autopsy of the animal the spleen is also found studded with tubercles. If the injection is intra-peritoneal, the superficial nodes may escape and the result must be determined by autopsy. In every case smears from

the lesion must be examined for tubercle bacilli. The importance of this has been emphasized in our own experience by the occurrence of an epidemic among our guinea pigs, which is characterized by nodules in the spleen not to be distinguished in the gross from tubercles; even histologic examination of these lesions may leave one in doubt. The disadvantage of animal inoculation is the time which must elapse before a conclusion can be reached, being usually six weeks when the result is positive. Many methods have been devised to shorten this period. Bloch recommended subcutaneous injection after crushing the inguinal nodes, a method which is supported by v. Illyés. Meyer claimed that the subcutaneous injection of 0.5 c.c. of old tuberculin into the inoculated animal may lead to the death of the animal or to a specific rise in temperature, the time required for a positive diagnosis being shortened by such an injection. Oppenheimer injects the sediment directly into the liver, believing that this method is quicker and more certain than subcutaneous or intra-peritoneal injection. The animal is killed at the end of 14 days, and the lesions of the liver and spleen are examined for tubercle bacilli. If the material is contaminated with other bacteria, this procedure may lead to the death of the animal before there has been time for the development of tuberculous lesions. The simultaneous injection of a concentrated broth filtrate from a tubercle bacillus culture with the sedimented material has been tried; our limited trials of this method have not proven it to be of any special advantage. Morton claimed that subjecting the guinea pig to a massive dose of Roentgen-ray just before or just after the injection of the suspected urine so lessened the resistance of the animal that lesions are obtained which permit a positive diagnosis in 8 to 10 days. Eckford found repeated small doses to be better than a single large dose, but admitted that "rapidity of appearance and development of the nodules depended more on the size of the dose of tubercle bacilli than upon the amount of *x*-ray given." He advised the removal of an inguinal node at the end of two weeks, the animal to be kept alive for the further development of internal lesions. Kellert's results with the Roentgen-ray were diametrically opposed to those of Morton. He found that the resistance of the animal is not decreased and that the method has no practical value. Susceptibility to contaminating or secondarily invading bacteria may be increased and lead to the death of the animal before tuberculous lesions have had time to develop. Corper has repeated a number of the methods which have been proposed for the purpose of hastening the diagnosis in the inoculated animal. He finds that inguinal gland crushing with subcutaneous injection has no appreciable effect, that lamp black injected subcutaneously coincidentally with the bacilli has a distinct retarding effect, and that finely pulverized glass has a slight accelerating action but not enough to make this method available for practical use. A method which will shorten the time necessary for the development of diagnostic lesions in the inoculated animal would be of the greatest help, but we must

conclude that none of the methods thus far proposed has yielded results which would warrant its unqualified acceptance.

Cystoscopy and Ureteral Catheterization.—The great aid of these procedures in the diagnosis of renal tuberculosis in adults is firmly established. In children they are more difficult of application, but if the age of the patient permits they should be tried. Rocher and Ferron say that ureteral catheterization should be easy in girls over five years of age. Oraison says that the procedure is easy in girls of six years and that he has been able to catheterize the ureters in a boy of seven years. Hyman has summarized the experience at the Mt. Sinai Hospital, New York, with these procedures in 30 children under nine years of age. The youngest boy cystoscoped was 14 months old; the youngest boy whose ureters were catheterized was "under three years" and the youngest girl was 22 months old. Ureteral catheterization with chromoscopy and functional tests is of the greatest importance in determining the side involved and the condition of the uninvolved kidney. In 155 cases of renal tuberculosis collected by Pollak, there were only 12 which failed to show a difference between the two kidneys by chromocystoscopic methods. In a case reported by Buerger the diagnosis was made by histologic examination of a bit of bladder mucosa removed from near the mouth of the ureter through the cystoscope.

Roentgen-ray Examination.—Direct Roentgen-ray examination of the kidneys may be of aid if calcium deposition has occurred, and Colston and White recommend that such an examination should be made before proceeding to cystoscopy or pyelography. The Roentgen-ray findings may be particularly valuable in those cases in which the ureter has been closed off, the group of cases in which the results of urinary examination may not be of much aid in diagnosis. Söderlund has reported a case of renal tuberculosis in a boy of 13 years in whom the diagnosis could be established only by Roentgen-ray. If the ureters can be catheterized pyelography may be helpful; v. Lichtenberg and Dietlen claim that the Roentgen-ray picture obtained by this procedure is typical.

Exploratory Incision.—If renal tuberculosis appears probable but the diagnosis cannot be definitely established by the means given above, exploratory lumbar incision is justifiable. Especially in children, in whom it may not be possible, because of the failure of ureteral catheterization, to determine which kidney is involved, this may be necessary. In a series of 166 cases of renal tuberculosis, Rovsing practiced lumbar incision 30 times and established the unilateral character of the condition 24 times. Kidd has exposed the ureter by exploratory incision in order to detect thickening and thus determine the side involved.

Palpation.—If the kidney is enlarged, it may be palpated. Deep palpation may elicit pain on the involved side, even when enlargement cannot be detected. In some cases in which it was impossible to

determine the affected side by ureteral catheterization, Kidd was able to palpate the thickened ureter through the vagina or rectum.

Treatment.—Upon few questions in medicine are opinions so well in accord as upon the treatment of unilateral chronic tuberculosis of the kidney. Very few agree with Karo in his belief that medical treatment should be tried first and that nephrectomy is indicated only when there is evidence of caseation, destruction of the kidney, or invasion of the bladder. Much more general is the opinion that the affected kidney should be removed as soon as a diagnosis of tuberculosis is established and the plea of all is for the earliest possible diagnosis. This opinion is based upon the study of spontaneous cure as compared with the results obtained after nephrectomy. That healing may occur spontaneously must be admitted to be a possibility, but those who have investigated the subject are skeptical as to its occurrence with enough frequency to influence treatment in an individual case. Apparent clinical arrest may occur, especially after occlusion of the ureter, but bacilli may still appear in the urine from time to time and the other kidney may be finally involved, as pointed out by Heitz-Boyer. Carrero believes that real cure probably does not occur; that even when the kidney is completely transformed into a caseous and partly calcified mass the disease is locally progressive. Rochet doubts the adequacy of the proof of spontaneous cure. v. Rihmer operated upon three cases of so-called spontaneous cure. These were cases of solitary tubercle of the kidney, with no other detectable foci in the body; the process was still active at the periphery of the renal lesion. Alessandri, upon the basis of two operative cases, considers the reported cases of healing doubtful. Rafin has analyzed 168 cases of unoperated renal tuberculosis. The average duration of the disease was a little over 4½ years, being somewhat longer in men than in women; 94 per cent. died of tuberculosis; of these, 17.5 per cent. died of generalized tuberculosis, 20 per cent. of tuberculosis of the lung and larynx, and 8 per cent. of tuberculous meningitis.

Conclusions as to operative results must be based upon adult cases, but probably hold also for children. Legueu and Chevassu tabulated 1539 nephrectomies from the statistics of 23 surgeons, with an early mortality of 5.9 per cent. In 708 cases with detailed reports the total mortality was 21.3 per cent., of which 6.1 per cent. were early deaths and 15.2 per cent. late. Of the latter group, a total of 108 cases, 75 died of tuberculosis. 78.7 per cent. of the 708 cases were living at the time of reporting and of these 41.2 per cent. were completely well. Of 738 cases treated medically 61.8 per cent. died and 38.2 per cent. were living for periods of 1 month to 10 years at the time of reporting. Of 71 patients subjected to nephrectomy by Krönlein in a period of 18 years, 53 were living at the end of the period of observation. The early mortality was 5.6 per cent. Of the 18 who died, 14 died during the first year after operation of miliary tuberculosis; the death of the remaining four cases occurred 4 to 10 years after operation. The

results of nephrectomy improve with the passage of time; if the remaining kidney becomes involved subsequent to nephrectomy, it is usually from a focus elsewhere in the body. In a series of 203 cases operated upon at the Mayo Clinic, reported by Braasch, there was an immediate mortality of 3 cases; 75 per cent. were considered permanently cured. Suter operated upon 60 cases, with an early mortality of 1.6 per cent. and a later mortality of 6.6 per cent.; one-half year after operation 56 per cent. were considered fully cured, 34 per cent. much improved, and 10 per cent. slightly improved. In Zuckerkandl's series of 104 cases, there were 7 early and 13 late deaths; of the 84 living patients, 45 were completely cured. v. Illyés, in 136 cases, had an early mortality of 4.5 per cent. and a late mortality of 17.4 per cent. In such statistics the operative mortality is low; the early deaths are usually the result of tuberculosis elsewhere in the body; all are agreed that the earlier nephrectomy is done, the better are the later results. If the ureter and bladder are already involved at the time of nephrectomy, the lesions usually become quiescent or disappear after removal of the kidney. Vignard and Thévenot say that in children the operation has a low primary mortality and that there is apparently complete recovery in the majority of cases. According to Wildbolz, non-surgical treatment is justifiable only in early bilateral involvement, or when a unilateral lesion cannot be safely operated upon because of some lesion elsewhere, or when tubercle bacilli are found in the urine but pus is absent.

Even bilateral renal involvement is not an indication against removal of a markedly affected kidney if the other shows only slight functional impairment. Thirteen cases with bilateral involvement were operated upon by Rochet and Thévenot; of 11 cases with one kidney greatly involved and the other slightly, five died in three weeks to two years; the remaining six, living after two years, were in an improved condition. They advise against operative interference if both kidneys are only slightly involved or are in an advanced stage of the disease; in the former, medical treatment should be tried; in the latter, the prognosis is hopeless. Ekehorn (quoted by Wagner) advises removal of the primarily involved kidney if it has practically no functional value and is having a harmful effect on the general condition; five of his six nephrectomized cases were improved.

Blood may appear in the urine from a supposedly sound kidney after the removal of its tuberculous mate. Peña finds that this may be due to the congestion associated with compensatory hypertrophy; to tuberculosis which was present but not recognized before operation and which becomes worse as the result of operation; to non-tuberculous infection; to hemorrhagic nephritis. He advises a guarded prognosis in such cases.

SYPHILIS OF THE KIDNEY

Syphilitic involvement of the kidney, when it occurs in children, is a part of the congenital form of the disease in the great majority of cases. Clinical evidence does not indicate the occurrence, in the course

of syphilis, of any form of nephritis which is symptomatically characteristic, nor does it indicate any great frequency of urinary abnormalities in syphilis. This is all the more striking when the almost constant localization of treponemas in the kidneys in fatal cases of congenital syphilis is borne in mind.

Pathology.—The tissue reactions of the kidney to antenatal syphilitic infection have formed the subject of numerous careful studies. The kidney is frequently involved, in 90 per cent. of a series of 29 cases examined histologically by Hecker; this figure is all the more striking when compared with those for the other organs whose

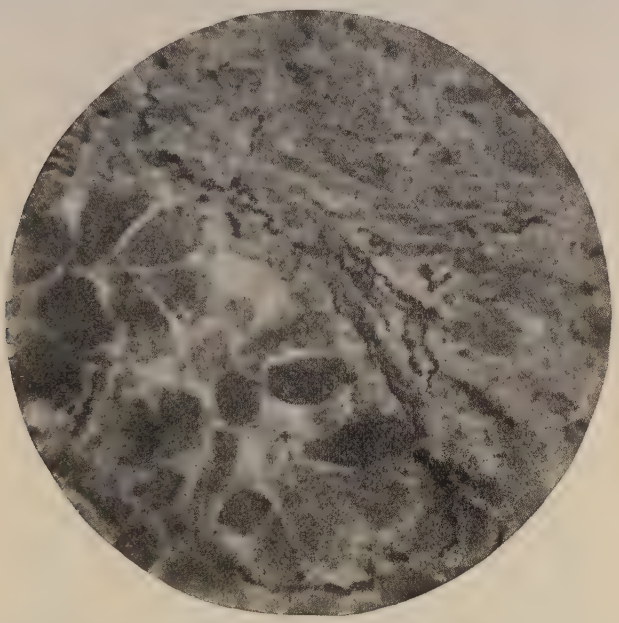

Fig. 169.—Treponemas in and about a glomerulus in a case of neonatal syphilis. Inflammatory reaction is absent. Photomicrograph. × 1500.

involvement in syphilis is considered so characteristic of the disease: Spleen, 61 per cent.; bone, 43 per cent.; liver, 23 per cent.; lung, 17 per cent. In premature, stillborn infants the kidney may show only a surprising richness in treponemas (Figs. 169, 170), without any tissue reaction (Versé, Schultz). Such a condition is probably the result of the overwhelming of the fetus by organisms in such numbers that fetal death occurs before the tissues have time to react. In other stillborn infants the number of organisms is small and the interstitial tissue of the kidney has reacted by proliferative or infiltrative changes (Fig. 171). In such cases it is necessary to suppose that the infection has been present for a longer time and has been less intense from the beginning. In those children in whom the grade of infection permits

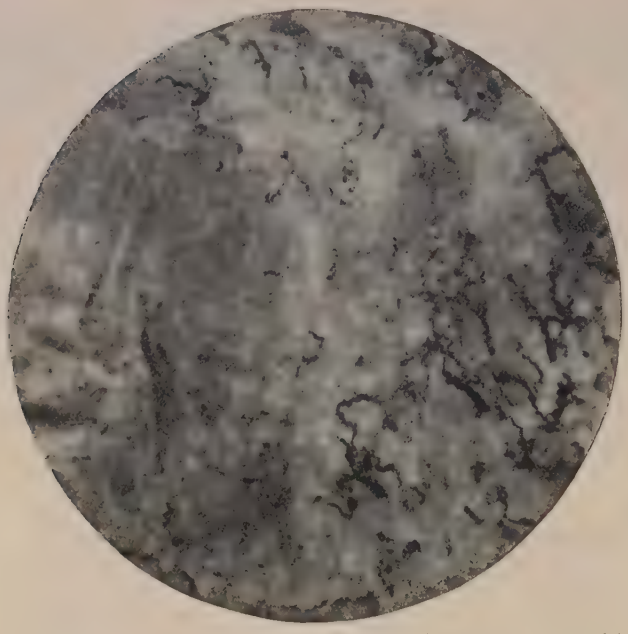

FIG. 170.—Numerous treponemas in the periarterial tissue of the kidney from a case of neonatal syphilis. Photomicrograph. × 1500.

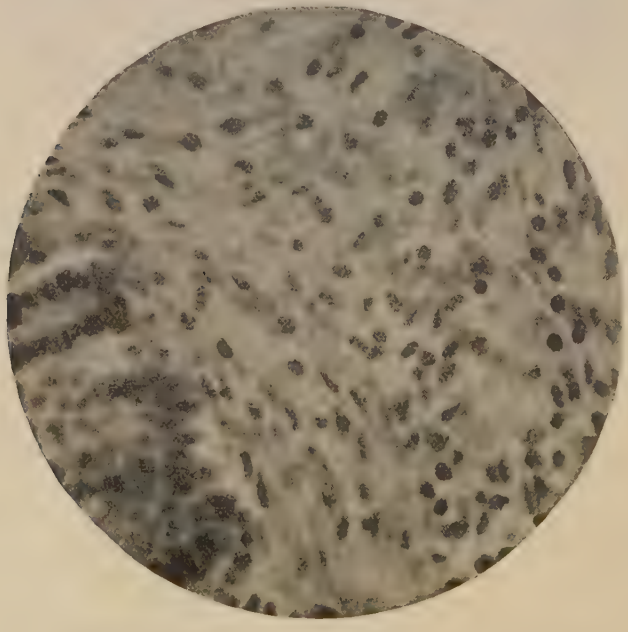

FIG. 171.—Increase and lymphoid infiltration of periglomerular interstitial tissue. In this kidney there was marked interstitial reaction with a few treponemas. Photomicrograph × 600.

a variable duration of life after birth, the kidney may be the seat of quite marked pathologic changes at autopsy. Most common is a diffuse interstitial inflammatory process, characterized by lymphoid infiltration and increased richness of the interstitial tissue in young fibroblastic cells, to which the name diffuse subacute interstitial nephritis may be applied. A probable diagnosis of syphilis can be made only if the blood-vessels show suggestive changes (Schultz), a certain diagnosis only if the specific organism can be detected in the kidney. The diffuse process may be associated with the formation of miliary or larger gummas; calcification may occur in the gummas (Mathewson). The parenchymatous elements may show very little change and in the gross such a kidney varies little from normal. In certain cases, and these are the more interesting from the clinical standpoint, the kidney is slightly enlarged and pale and has the gross appearance of an acute parenchymatous nephritis. In such cases there is degeneration and sometimes proliferation of the tubular epithelium, in addition to more diffuse inflammatory changes. At times there may be hemorrhage into the tubules of a degree sufficient to warrant applying the name acute hemorrhagic nephritis to the condition. Finally, there may occur in children with a previous history of congenital syphilis a type of renal involvement characterized by decrease in the size of the organ and by chronic interstitial fibrotic changes; the proof that such a chronic interstitial nephritis is specific in origin or in nature is not always easy to adduce. If one demands the presence of the specific organism as a criterion of syphilis, the number of such cases in which the syphilitic nature of the chronic interstitial nephritis has been established is very small. In addition to these various inflammatory conditions which may be due to syphilis, the disease has also been held responsible for maldevelopments of the kidney. A condition in whose causation syphilis is believed by Karvonen, Hecker, Cassel, Störck and others to play a part is characterized by the persistence of fetal nephrogenic tissue in the cortex, with decrease in the number of glomeruli and tubules. That this non-inflammatory process is due to actual localization of treponemas in the kidney appears improbable. In fact, much of the literature relating to the histopathology of congenital syphilis must be carefully weighed if it antedates the discovery of the parasite or Levaditi's classical study of the localization of the organisms in the tissues. Moderate degrees of renal hypoplasia, like those ascribed to lues, may be part of the poor general nutritional condition which antenatal infection causes, and pure parenchymatous changes without interstitial inflammatory reaction may possibly be due to a toxic action. In neither case would it be proper to consider the resulting condition actually specific.

Symptoms.—Although in fatal cases of neonatal lues the kidneys may show marked pathologic changes, it is remarkable that our knowledge of the clinical manifestations of this process is so indifinite. This may be due in part to the fact that the disease progresses so rapidly

in some cases that the more striking phenomena of nephritis, such as edema and uremia, do not develop; in part it may be due to the slight degree of attention which is usually paid to the urine of the very young infant. When the possibility of syphilitic renal involvement is kept in mind and the urine is examined for the purpose of detecting any changes which might be ascribed to the luetic process, extreme caution is necessary in interpreting the results. Antisyphilitic treatment vitiates the conclusion, because the nephritis, if the urine shows any evidence of it, may be due to therapy rather than syphilis. Or minor associated conditions such as intestinal or other infections may cause the appearance of albumin in the urine. In order that a nephritis may justly be ascribed to syphilis in any given case, most writers demand that the possibility of renal change by drugs or by infections other than syphilis be excluded. To these we might add that the specific nature of the process in the kidney must be definitely established at autopsy by the presence of the treponema in the renal tissue.

Hahn in 1912 submitted the previously reported cases of supposed syphilitic nephritis to critical review. He could find only eight cases of acute and subacute interstitial nephritis in which the results of urinary examination are recorded; in seven of these the urine was normal; in one albumin was present in a specimen examined shortly before death. That there are no urinary changes in such cases may be due to the slight involvement of the tubular epithelium and glomeruli in the interstitial process. Of cases of chronic interstitial nephritis, only those of Massolongho and Carpenter are accepted as being syphilitic in nature. Acute parenchymatous nephritis, leading to the presence of albumin and of granular and hyalin casts, is held by Hecker to be fairly frequently due to syphilis. Of cases of this kind Hahn accepts only those of Bradley, Carpenter and Audéoud; in these the urine contained much albumin, casts were present, and there was edema of the face and extremities. Similar urinary findings with the additional presence of red blood corpuscles have been held to indicate an acute hemorrhagic nephritis; in most of the reported cases these evidences of renal involvement have appeared only after the beginning of mercurial treatment. Hahn holds that in only two of the previously reported cases can the acute hemorrhagic nephritis be safely ascribed to syphilis. He himself added three cases, one of which is doubtful because antiluetic therapy may have been a factor.

Hintzelmenn made a clinical study of a rather large series of cases of congenital syphilis to determine the possibility of renal involvement. Of 41 nurslings with syphilis, 27 gave negative urinary findings; in 14 the urine contained albumin, granular or hyalin casts, and leukocytes. Of this last group of 14, all but three had recently received or were under treatment. Twenty-eight older syphilitic children were examined. In two, who had been untreated, the urine was negative; 15 had been treated at a period previous to the urinary examination; the latter was negative. Eleven were under intensive

treatment at the time of examination; albuminuria appeared in two of these during the course of treatment; in only one of the entire 28 cases were there urinary changes indicative of nephritis, in this case a chronic interstitial nephritis held to be due to syphilis.

Jeans, in a discussion of late hereditary syphilis, records a single doubtful case of syphilitic chronic interstitial nephritis, and questions the ability to establish clinically the luetic nature of nephritis in infancy. Guthrie believes that interstitial nephritis in childhood may be due to syphilis, but admits the difficulty of satisfactorily establishing the luetic nature of the process. All are agreed that the course of chronic interstitial nephritis supposedly due to lues is exactly like that form in the causation of which syphilis can be excluded. Treatment of the acute and subacute forms is complicated by the further injury which antiluetic therapy may do to the already damaged kidney. Hutinel, Guthrie and others emphasize the danger of mercury. Hintzelmann considers calomel by mouth to be less dangerous than mercury administered by inunction or hypodermatically. The arsenic compounds also are not entirely without danger if the kidney is already damaged.

AMYLOID DISEASE OF THE KIDNEY

Amyloid, a compound of protein with chondroitin-sulphuric acid, does not occur normally in the body. Its nearest normal analogue is found in the ground substance of cartilage and yellow elastic tissue. While there has been controversy as to whether amyloid deposition is an infiltration or a degeneration, the former is the prevailing view today, and it is believed that the material is deposited as the result of the union, outside the blood vessels, of some constituent derived from the blood with another constituent derived from the tissues. The deposition begins just outside the endothelium of the capillaries. As it increases, the capillary lumen is compressed and finally obliterated, and the surrounding tissues are atrophied by pressure. The substance may be laid down also in the walls of the small veins; the arteries are less frequently involved. With watery solutions of iodin, amyloid gives a brownish-red color in the gross when applied to the fresh tissue; in sections treated by the proper methods the staining reaction is characteristic. The infiltration is associated with long continued suppuration or destruction of tissue and occurs most often in chronic osteomyelitis and chronic bone tuberculosis; it may occur in chronic leukemia.

In the kidney the change occurs first in the glomerular capillary loops, in the afferent vessels of the glomeruli, and in the intertubular capillaries of the cortex and medulla. Finally, the material may be deposited just outside the basement membranes of the tubules. Usually it is part of general amyloid disease, in which the changes are most marked in the liver and spleen. Rarely amyloid infiltration may occur locally in the kidney as the result of chronic interstitial nephritis, but then only in such small amounts as to have little influ-

ence upon the gross or microscopic picture. In the typical kidney of general amyloid disease the organ is enlarged, increased in consistency with a rubber-like feel, pale with often a wax-like semitranslucence. The cortex is thickened and the medulla is of a deeper color than the cortex. Microscopically entire glomeruli may be replaced by homogeneous, non-nucleated, glassy, eosin-stained material. Similar material is present in the intertubular tissue and about the tubules themselves. The involved tubules undergo compression atrophy, and by vascular obliteration the nutrition of the rest of the kidney tissue is interfered with. As a result, the amyloid kidney is usually also the seat of parenchymatous degenerative changes and of a chronic inflammatory interstitial process.

The urinary changes suggest both chronic parenchymatous and chronic interstitial nephritis. The urine quantity is increased, the color is pale and clear, and the specific gravity is low, changes suggestive of the last-named form of nephritis. In common with parenchymatous nephritis, albumin is usually abundant and globulin may be present. Sometimes the albumin is low in amount or absent, the variation in this respect depending possibly upon the degree of interstitial change and upon the localization of the amyloid deposit. Hyalin, fatty, granular, or waxy casts may be present. Dropsy is a variable symptom. The urinary changes are not characteristic and usually do not of themselves permit a diagnosis of amyloid kidney. The associated general condition and enlargement of the spleen and liver aid the diagnosis. Rist and Kindberg, who made a correlative anatomical and chemical study of amyloid kidney in tuberculosis, say that amyloid infiltration may be present before there are any urinary changes. Albuminuria and polyuria may be the first symptoms. A syndrome which they consider characteristic is decrease in blood urea and a serum chlorid content below the normal threshold of excretion, associated with normal excretion of urea and chlorides. These changes are interpreted as an exaggeration of the concentrating powers of the kidney, that is, a sort of hypersecretion.

ANIMAL PARASITES OF THE KIDNEY

The kidney is an infrequent site of localization of animal parasites. Of these, the one which is most often encountered is the cystic stage of the hydatid tapeworm, Echinococcus granulosus (Tenia echinococcus). In the larger tabulations of hydatid disease in adults the kidney ranks third in order of frequency, being preceded by the liver and the lungs in the order named. For a discussion of the relative frequency of hydatid disease in children, as compared with adults, the reader is referred to the chapter on "Echinococcus of the Lung." The development of the cyst in the kidney leads to enlargement of the organ. On palpation a mass may be felt, which may be either smooth or lobulated. The condition may exist apparently for years without causing symptoms and the dead, encapsulated cyst may be a chance

post-mortem finding. More often the cyst ruptures into the pelvis of the kidney. The passage of pieces of cyst membrane or of daughter cysts may lead to intense renal colic or may be without symptoms. Rupture may be followed by healing, by the continued growth of the cyst with passage of its contents, or by suppuration.

In the differential diagnosis of renal hydatid, hydronephrosis offers the greatest difficulty. The condition must also be differentiated from cystic kidney and from ovarian or parovarian cyst. If pieces of cyst membrane, scolices, or daughter cysts are present in the urine or in puncture fluid, the diagnosis is established. Complement fixation is of doubtful value. The treatment is surgical, either incision with free drainage or nephrectomy. Some recommend palliative measures if the cyst has ruptured and if rupture is not followed by colic and by impairment of the general health.

Other animal parasites involve the kidney so rarely as to be curiosities. The cysticercus stage of the pork tapeworm, Tenia solium, has been reported in the kidney. In rare cases of bilharzia disease the eggs of the parasite, Schistosomum hematobium, may set up an inflammatory reaction in the kidney. Dioctophyme renalis (Eustrongylus gigas), the kidney worm, is the largest of the nematodes affecting man. It occurs usually in the kidney, and two, three, to as many as eight worms may be present. It may be present without symptoms, or it may lead to hematuria or to obstruction of the kidney; the ova are characteristic and may be found in the urine. Although the geographic distribution of this parasite is wide, only a small number of cases of human infestation is on record. Porocephalus (Pentastoma) denticulatus, the larva of Linguatula rhinaria, is said to occur occasionally in the kidney.

INJURY OF THE KIDNEY

Injury of the kidney in children is usually the result of contusion, due to a blow, to a fall upon some hard object, or to being run over by a vehicle. Puncture wounds are rare. In contusion injuries the kidney itself may show contusion of its tissue, laceration of varying degree, or complete rupture with separation of the kidney into two equal or unequal parts; without rupture of the capsule the entire renal tissue may be disorganized by intracapsular hemorrhage, as in De Forrest's case. Injury to the skin may be absent or slight. The usual immediate result of an injury of any of these grades is hemorrhage. The latter may be interstitial and limited to the kidney, it may be retroperitoneal, or it may be intra-peritoneal. Hematuria is the most striking symptom, but is not always an indication of the degree of injury which the kidney has sustained or of the site of the injury (Cathelin). Hematuria may be absent in the more severe injuries, just those in which surgical intervention may be necessary. In such cases the general condition, such as shock and evidence of hemorrhage, or progressive

lumbar swelling must be the guide to the treatment. Shock may be absent (Bloch).

The treatment of subcutaneous injury should be conservative unless there are definite indications for surgical intervention. In a series of 57 cases reported by Ponomareff, the kidney was subjected to operative interference only three times, twice for purulent involvement and once because of decreasing urine volume. The total mortality in this series of conservatively treated cases was 3.7 per cent. (two cases); in neither case was death due to the renal injury alone. Michelsson reported 30 cases of rupture of the kidney treated expectantly with only three deaths; in the fatal cases there were severe complicating injuries. Gibson, who added four cases of traumatic rupture to the 22 reported cases of subcutaneous injury of the kidney in children, advises against operation in cases with no very severe symptoms and in those with severe generalized injury with bad general condition and no urgent renal symptoms. In cases where operation is necessary, nephrectomy should be reserved for those in which the integrity of the kidney can not be preserved, or if hemorrhage can not be controlled otherwise, or if the outflow of urine into the ureter can not be restored. Suter tabulated 701 subcutaneous injuries of the kidney; the total mortality was 18.6 per cent.; in 131 treated by nephrectomy the mortality was 16.7 per cent.; in 143 conservative operations it was 14.6 per cent.; 20.6 per cent. of 427 treated expectantly died. Mason, as the result of his own experience and the published results of Neilson Watson and Connell, favors immediate operation, unless the local symptoms are very slight and constitutional symptoms are absent. From his experimental work on dogs, Falcone warns that conservative treatment of kidney injuries may be harmful. He found that albumin and casts may appear in the urine of the uninjured kidney, which anatomically may show hemorrhage, inflammation, degeneration, and at a later stage sclerosis. These changes he supposed to be due to the action upon the normal kidney of cytolysins derived from the injured organ. Another explanation may be that the urinary and anatomic changes are the result of the work suddenly thrown upon the sound kidney before it has had time to undergo compensatory hypertrophy.

If intra-peritoneal rupture of the kidney or associated injury of some other abdominal organ is suspected, operation should not be delayed. Infection may necessitate operation at a later stage when there were no indications for immediate intervention. In a case reported by Esau, injury of the kidney to a child of 13 years due to a violent blow in the lumbar region, operation became necessary four weeks after the injury because of a large perirenal abscess. Later there developed a duodenal fistula, whether the result of the primary injury, of the suppuration, or of injury at the operation, it was impossible to determine. Most of the intestinal complications of renal traumatism are in the colon. Esau was able to find only two reported

cases of duodenal involvement, and one other involving the small intestine, the region not being stated. Late infection of the injured kidney may be hematogenous, ascending, or from the bruised intestine.

Another late complication of injury to the kidney is hydronephrosis, which, according to Wagner, usually occurs after weeks or months. In Lundén's case, a 3½ year old child, the hydronephrosis developed one week after a fall. Pseudohydronephrosis, due to the collection of fluid about the kidney, is an early manifestation. True hydronephrosis may be due to injury at the beginning portion of the ureter, to occlusion of the ureter by blood clot or pressure of periureteral exudate or hemorrhage, or to intra-capsular rupture of the kidney. Operation is advised when hydronephrosis develops, if there have been no previous indications.

Puncture or stab wounds of the kidney require immediate surgical intervention (Solowow), for the control of hemorrhage and for the prevention of fistula. If the bleeding can not be controlled by suture and ligation, nephrectomy may be necessary.

MALFORMATIONS OF THE KIDNEY

In its embryologic development the tissue which gives rise to the permanent kidney passes through a complicated series of changes, some of which are progressive, others regressive. The origin of the urinary system is intimately associated with that of the genital system. The vascular relations in that portion of the body in which the urogenital system arises are quite different in early fetal life from those of later fetal and post-fetal life; vessels which are prominent at the stage of development when the kidney is most susceptible to mechanical influences later become small or disappear completely. This combination of circumstances makes the kidney liable to developmental anomalies which can be understood only upon the basis of embryogenesis. The urinary system anomalies may be associated with abnormalities in the genital system; the vascular supply of the abnormal kidney usually deviates from the normal; and there may be associated developmental errors in the terminal portion of the intestinal tract. Many renal anomalies have been chance findings of the post-morten examination: some have been unfortunate discoveries made on the operating table. Cystoscopy, ureteral catheterization and roentgenography have greatly simplified the ante-mortem and pre-operative diagnosis of anomalies of the urinary system, so that today the proper diagnosis is made or should be made in a larger percentage of the cases in which, in earlier times, operative procedures were followed by unfortunate results.

Embryology of the Permanent Urinary System.—According to the studies of Pohlman, in the 4 mm. stage of the human embryo the lower end of the Wolffian body or mesonephric duct has reached and united with the relatively large cloaca, the posterior end of which is continued into the narrow blind caudal gut. At 5 mm. the renal bud

has been given off (Fig. 172) from the dorsolateral aspect of the Wolffian duct at a short distance cephalad to its cloacal end. At about 10 mm. the renal bud has grown into the undifferentiated tissue lying ventral to the lower end of the aorta. This tissue later becomes the renal mesenchyme, from which the secretory portion of the kidney is

Fig. 172.—Human embryo of about 5 mm. 1, intestine; 2, renal bud; 3, Wolffian duct; 4, allantois; 5, cloaca; 6, caudal gut. (After Huntington.)

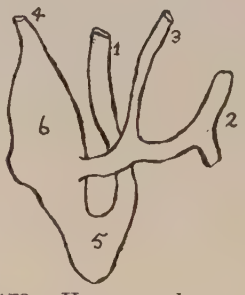

Fig. 173.—Human embryo of about 10 mm. 1, intestine; 2, renal bud divided into the two primary divisions of the pelvis; 3, Wolffian duct; 4, allantois; 5, cloaca; 6, bladder. (After Huntington.)

developed. The free end of the renal bud has divided into a cephalic and caudal branch, which form the primary subdivisions of the renal pelvis. The duct of the renal bud, which becomes the ureter, is still united with the Wolffian duct, which empties into the dorsal, caudal

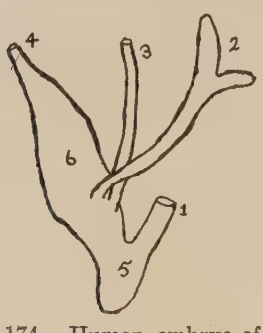

Fig. 174.—Human embryo of about 14 mm. 1, intestine; 2, renal bud, with the ureteral opening separate from that of the Wolffian duct; 3, 4, allantois; 5, cloaca; 6, bladder. (After Huntington.)

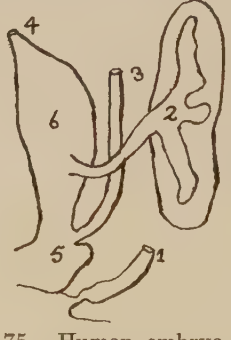

Fig. 175.—Human embryo of about 20 to 25 mm. 1, intestine; 2, renal bud covered by renal mesenchyme; 3, ejaculatory duct, which opens into the urogenital sinus, 5; 4, allantois; 6, bladder. (After Huntington.)

portion of the bladder, now partly separated off from the cloaca but still opening with the intestine into the remains of the cloaca (Fig. 173). At this stage the two renal buds lie very close to each other near the mid-line, behind the bladder in the sacral region, surrounded

by the relatively large umbilical and post-cardinal vessels; the Wolffian body is large. At about 14 mm. the ureter and the Wolffian duct have established separate openings into the bladder, that of the ureter being lateral and slightly cephalad to that of the Wolffian duct. Bladder and intestine still open into a common cloaca (Fig. 174). Division of the free, cephalic end of the renal bud has continued and has led to the formation of secondary calyces. The kidneys now lie opposite the mid-lumbar level. Axial rotation, which ultimately places the originally anterior or ventral hilum of the kidney on the mesial surface, has begun. At a somewhat later stage the cloaca has disappeared and the intestine and bladder have separate openings to the exterior. The opening of the Wolffian duct has been carried caudad to that of the ureter and as the opening of the vas deferens in the male comes to lie in the urogenital sinus or prostatic urethra (Fig. 175). The upward migration of the kidney, which is aided by regressive changes in the Wolffian body, has continued, the normal renal level being reached at the 25 to 30 mm. stage of the human embryo. The vascularization of the kidney is effected after the organ reaches its permanent position. The complicated series of changes through which the urogenital system passes gives opportunity for a variety of permanent developmental anomalies whose embryogenetic explanation has been considered by Huntington.

Frequency.—An accurate estimation of the frequency of anomalies of the kidney and ureter cannot be given, because minor anatomic variations, such as partial duplication of a ureter or fetal lobulation, which are frequent, receive little consideration in the literature. Neumann (quoted by Heiner) found 100 congenital renal anomalies recorded among 10,177 autopsies done at Kiel. Adrian, in 411 admissions to the Strassburger Poliklinik für Harnkranke in the course of one year, encountered seven anomalies, as follows: Complete unilateral double ureter, three; renal dystopia with hypoplasia, one; absence of one kidney, one; horseshoe kidney, one; hydronephrosis due to accessory artery, one. At the Mayo Clinic, in the five years preceding 1912, there were 36 patients with ureteral or renal anomalies (Braasch). This number included seven cases in 171 autopsies (4 per cent.). Twenty-five examples of anomaly were encountered in 649 operations on the kidney and ureter (1 in 26). The anomalies found were as follows: Fused or horseshoe kidney, 11; single kidney, six; atrophic (hypoplastic?) kidney, five; ectopic kidney, three; duplication of pelvis and ureter, eight; division of ureter, five. Bugbee and Losee recognized 23 anomalies in 10,000 urologic examinations, as follows: Dystopia of kidney, six; horseshoe or fused kidney, three; single kidney, two; hypoplasia, one; duplication of pelvis, six; duplication of ureter, five. For certain of the anomalies there are more complete statistics, which will be referred to later.

Classification.—For the purpose of the discussion which is to follow, the anomalies to be considered are classified as follows, the

classification being based upon embryogenetic features as much as possible.

I. Anomalies of number:
   (*A*) Excess:
      1. Duplication of ureter and pelvis.
      2. Duplication of kidney.
      3. Accessory or supernumerary kidney.
   (*B*) Defect:
      1. Absence of kidney.
II. Anomalies of form and size:
   1. Hypoplasia of kidney.
   2. Lobulation of kidney.
   3. Discoid kidney.
   4. Hypertrophy of kidney.
III. Anomalies of position:
   1. Vertical dystopia.
   2. Horizontal dystopia.
IV. Fusion anomalies:
   1. Polar fusion without dystopia.
   2. Lateral fusion without dystopia.
   3. Fusion with dystopia.
V. Vascular anomalies.
VI. Anomalies of ureter other than increase or decrease in number. Hydronephrosis.

Reduplication of Ureter and Pelvis.—Embryogenetically this is the simplest of the urinary tract malformations. The cephalic end of the renal blasteme normally divides at a very early stage into a cephalic and caudal portion, which become the superior and inferior primary calyces of the normal pelvis. Incomplete division of the pelvis into two main portions falls within the range of normal variation. If the normal bifurcation is exaggerated or if it begins while the renal bud is still very closely attached to the Wolffian duct, then there may occur grades of reduplication which vary from complete double pelvis with a single ureter to two ureters which are entirely distinct and have separate inferior openings. The formation of two pelves must be considered the simplest form of reduplication, and partial or complete doubling of the ureter must always be associated with duplication of the pelvis. In the intermediate condition of incomplete doubling of the ureter, the two branches may be separate for a variable distance from the kidney, but open into the bladder by a common orifice. The two ureters may run in the same sheath and appear externally as a single ureter; or the reduplication may be apparently complete, the union occurring in the intramural portion of the ureter (Fig 176). The condition may be unilateral or bilateral; in the latter case it may be incomplete or complete on both sides, or complete on one side and incomplete on the other.

When the reduplication is complete interesting and clinically important possibilities arise as to the ureteral openings into the bladder. If the longitudinal division of the ureter extends to the bladder at a stage when ureteric duct and Wolffian duct have become separated from each other, the two ureteral orifices may lie very near each other in the trigonal portion of the bladder. The opening of the

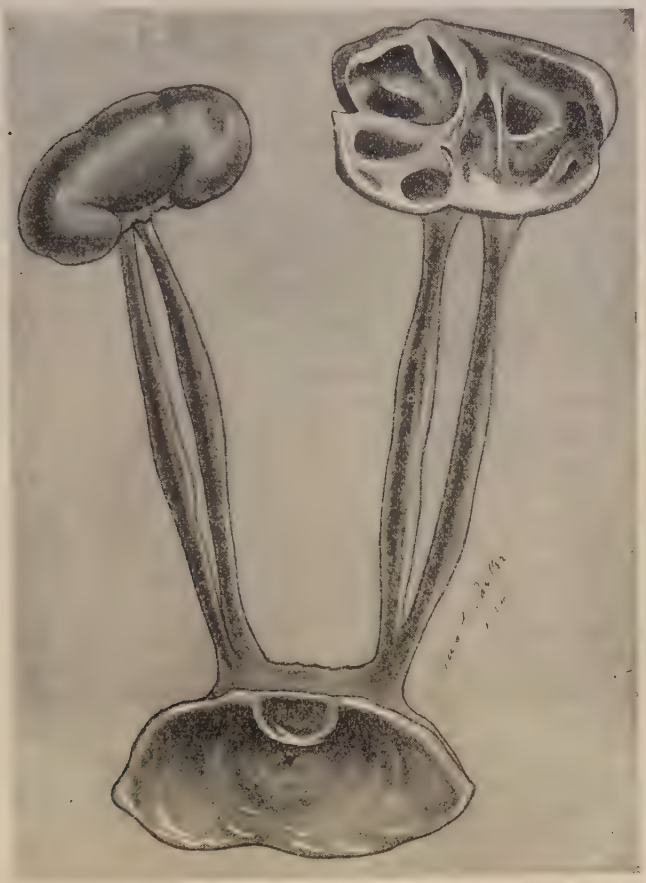

Fig. 176.—Reduplication of ureters with hydronephrosis. (From the collection of Dr. I. A. Abt.)

ureter from the lower pelvis always occupies the situation of the normal ureteral orifice. That of the ureter from the upper pelvis always lies mesial or caudal to that of the ureter from the lower pelvis. If the division proceeds to the bladder while Wolffian and ureteric ducts are still united, then the ureter from the upper pelvis may be carried far downward into the genital tract by the migration of the Wolffian duct. One ureter may therefore open with the ejaculatory duct into

the prostatic urethra, as in the case included by Huntington in his series. Or it may not open into the urinary tract at all, but may have a separate opening, as in the case reported by Pieri. In this case, a girl of 16 years, urine escaped from an opening situated to the right of the urethral meatus; a right ureteral orifice into the bladder could not be found on cystoscopic examination. From the right kidney, removed by nephrectomy, two ureters were given off which united at a distance of about 8 cm. from the kidney, from which point the single ureter ran to the external opening mentioned. Hartmann reported a similar case, in which the orifice of a supplementary ureter from the right kidney lay just beneath the external urethral meatus. He was able to collect 37 cases of extravesical termination of the ureter in the female. Six times the ureter opened into the urethra, eight times into the vagina, 21 times into the vestibule, and twice into Gärtner's duct. Cystic dilatation of the aberrant ureter was frequent. In Stammler's case, a girl of 15 years, there was bilateral complete reduplication of the ureters, as determined by roentgenographic examination and ureteral catheterization, one ureter on each side opening into the urethra. If the ureteral orifice lies below the bladder sphincter, incontinence of urine is the symptom which brings the case to medical attention. Rarely, an accessory ureter may end blindly in the bladder wall beneath the mucosa, leading to cystic protuberance of the bladder wall and to hydronephrosis. Of the utmost clinic importance is the fact that there has apparently been no exception to the two rules formulated by Weigert in 1877: (1) The lower of the two ureteral orifices, lying on the same side of the body, belongs to the upper ureter; (2) of two orifices lying in the same horizontal plane, the mesial one belongs to the upper ureter.

Partial reduplication of the ureter is an anomaly of frequent occurrence. Six cases, reported by Pawloff, occurred in 200 kidney operations (3 per cent.). According to him, the frequency varies, in different statistical collections, from 1 per cent. of all cases (Krause) to 10 per cent. (Weigert). Of his six cases, one was bilateral, four were of the right side and one was of the left side. In Wimmer's series of 12 cases, the condition was bilateral once, present on the right side six times, and on the left side five times. Meyer, who studied the anomaly in fetuses of the latter half of pregnancy, found eight cases in the material collected in the course of a year; in three of these the reduplication was bilateral.

Ureteral reduplication may lead to hydronephrosis of one pole of the kidney, if a ureter becomes obstructed by the abnormality of its course or if it ends blindly in the bladder wall. Usually it is the upper pole which is involved, because the course of the upper ureter is less direct than that from the lower pelvis. If a ureter opens into the vagina or below the bladder sphincter, ascending infection may lead to pyonephrosis of the upper part of the kidney. Resection of only the involved portion of kidney is advised, unless infection

has damaged the entire kidney. For ureters which open below the sphincter transplantation into the bladder has been tried. In Stammler's case of this kind, the aberrant ureter was ligated and the two pelves were anastamosed.

Reduplication of Kidney.—The genesis of this condition is the same as that of ureteral reduplication, and what has been said in regard to the course of doubled ureters applies to the ureters of double kidneys. The primary normal bifurcation of the renal bud occurs early and is carried more deeply into the bud than normal and each becomes covered with a more or less independent mass of secreting tissue of the renal mesenchyme. In most of the reported cases the renal reduplication is not complete, the two portions of the incompletely divided kidney being united by fibrous tissue. That the condition is due to abnormal division of the single original renal bud rather than to the formation of an accessory bud is proven by the fact that each portion of the anomalous kidney is smaller than a normal kidney. Usually the superior (cephalic) portion is smaller than the inferior. Since, as has been pointed out above, the cephalic ureter is the one which takes an abnormal course, the superior portion of the reduplicated kidney is very apt to show pathologic changes, especially hydronephrosis. In Wimmer's series of 12 cases of ureteral reduplication, there was one case with bilateral renal reduplication. Suter reported two cases and collected 17 others from the literature. In the first of his own two cases, diagnosed before operation, there was a cystic protuberance of the bladder wall near the left ureteral orifice. This was the distended blind end of a ureter coming from a hydronephrotic renal mass closely attached to the upper pole of the left kidney; this mass had its own arterial supply direct from the aorta. In the second case, both portions of the left kidney, which were united by a layer of dense fibrous tissue, were hydronephrotic; each portion had its own pelvis and ureter. Of the collected cases, the condition was a post-mortem finding in four; in the remaining 13 cases the diagnosis was made before operation in only two. Colic and tumor were the most common symptoms; in several of the cases operated upon in the third decade of life, recurrent attacks of colic had been present since childhood. In Calabrese's case the lower portion of the kidney was the smaller. In Josephesons's case, an 18 year old girl, the ureter from the reduplicated upper portion of the left kidney opened into the vulva to the left of the urethral meatus. In the cases of Munro and Goddard and of Cheyne the supernumerary kidney was quite distinct and had a low position. In the case of Cobb and Giddings a papillary cystadenoma had developed at one pole of a kidney situated to the left of the vena cava and separate from the normal left kidney; a ureter from the abnormal kidney was not found. Schönberg has also reported a case in which the anomalous kidney was the seat of a tumor. Two ureters opened separately into the right side of the bladder. The lower led to a small normal kidney; the upper

came from an adenomatous mass attached by fibrous tissue to the upper pole of the small right kidney. In the 19 cases included in Suter's report, the reduplication occurred on the left side 11 times, on the right side seven times, and in one case it was bilateral. Eight cases were males, eight were females, and in three the sex was not stated. The most recent collective review of this subject is that of Eisendrath. Correct diagnosis, either before operation or during the course of operation, makes conservative treatment possible and may enable the surgeon to save the uninvolved portion of the kidney.

Supernumerary Kidney.—A small number of cases suggests the possibility that a renal mass distinct from the normal kidney, a supernumerary kidney, may be due to the giving off of an accessory renal bud from the primary one, rather than to abnormal division of the latter. This is the interpretation given by Huntington for one of his examples in which the formation of primary and secondary calyces was normal. The lower ureter came from a separate, lower lying pelvis. This process of accessory renal bud formation may be the explanation of the condition found in those cases where the reduplicated organ lies much lower than the normal kidney and is separate from the latter; the cases of Cheyne, of Munro and Goddard, and of Schönberg, mentioned above, are of this type. A similar case is credited to Blasius by Strube. In reduplication due to abnormally deep bifurcation of the original single renal bud, the anomalous renal mass lies at the upper pole of the kidney and the two masses are usually closely attached to each other and are of approximately equal size. The supernumerary kidney due to the formation of an accessory renal bud lies below a kidney of approximately normal size and position and need not be attached to the latter. Pawloff credits Malinotti with the report of a case in which there were five urinary bladders, five kidneys and six ureters.

Absence of the Kidney.—Absence of the kidney may be due to failure of formation of the renal bud, in which case the development of the renal mesenchyme may be interfered with and none of the renal elements need be formed. Or it may be the result of failure of development of renal mesenchyme, the renal bud being normally formed; in the latter case some indication of renal pelvis and ureter may be present and differentiation from congenital renal hypoplasia is difficult. In most of the cases of true absence of the kidney the fault has apparently been a failure of formation of the renal bud.

Bilateral absence of the kidneys is not compatible with life and is usually associated with other grave developmental anomalies. Natanson (quoted by Busse) has reported a case, a child which died 54 hours after birth, in which the kidney, renal pelvis and ureter of the right side were completely absent. The left kidney was represented by a small nodular body which was 1 cm. in length and was composed mostly of pelvis. The tissue between the rudimentary calyces contained many glomeruli and islands of cartilage. In this

case no renal bud had been formed on the right side. A renal bud had been given off on the left side and the presence of glomeruli indicates that the bud had become covered with mesenchyme, but the further development of the kidney was inhibited.

Absence of one kidney is of more frequent occurrence. Winter found 13 cases in 32,415 autopsies. The absence may be apparent or real. In the first case a kidney is absent on one side of the body, but the organ of the opposite side has two pelves and two ureters, the latter having normal orifices at the two upper angles of the bladder trigone. Such cases are examples of crossed dystopia with fusion and will be considered later. In true absence, the kidney which is present may have a single ureter which empties into the bladder on the same side as the kidney; or it may have two ureters, if reduplication has occurred, but both empty into the half of the bladder which corresponds to the side of the body in which the kidney lies. On the opposite side the kidney is absent. If a ureter has been formed and if the kidney is represented by a small mass of tissue, the condition is one of hypoplasia, which will be considered later.

The most comprehensive study of true absence of one kidney is that of Ballowitz, who reported three cases and collected 201 from the literature down to 1895; references which were not available would bring the number to that time to about 240 or 250 cases. From autopsy statistics he gives the incidence as 12 cases in 28,423 autopsies. In his 213 tabulated cases, the left kidney was absent in 117, the right in 88; the side was not stated in eight. Of the cases whose sex was given, 113 were males and 71 were females. The preponderance of left-sided absence over right-sided absence is striking in males, but does not appear to hold for females; in 112 male cases the left kidney was absent in 70, the right in 42; in 65 female cases, the left was absent in 31, the right in 34. The majority of the cases occurred in the ages between 21 and 50 years; in the fetus and newborn there were 23 cases; in the ages from 1 to 20 years there were 35 cases; from 51 to 70 years, 28 cases; above 71 years 8 cases. It must be remembered that the age given is that of the individual at the time the condition is detected; in all cases the anomaly had, of course, existed from the early embryonic period. In true absence of one kidney, the renal vessels of the side of the absent kidney are wanting. The ureter is usually absent. The present kidney is usually normal in shape and in position, but may be enlarged by compensatory hypertrophy. Ten years after the appearance of Ballowitz' paper Gérard was able to collect 278 cases of unilateral absence of the kidney. In his analysis the same preponderance of males over females and of left-sided absence over right-sided absence is apparent. In 136 cases the left kidney was absent, in 96 the right, and in 46 the side was not stated. One hundred and twenty-two cases were males, 93 females, and in 83 the sex was not given. The 278 cases of renal absence were included in a total of 527 congenital renal anomalies, thus forming over half of the reported anomalies. Heiner reviewed

the subject again 1908, added a case of absence of the right kidney in a male, and found reports of 10 cases in females and 16 in males not included in the previous tabulations of Ballowitz or Gérard. In the American literature the subject was reviewed by Radasch in 1908. Braasch's collection of 78 cases of renal anomaly at the Mayo Clinic in five years included six cases of unilateral absence. Adrian found one case in 411 admissions for urologic conditions. Bugbee and Losee had two cases in their series. Strube's report includes one case of absence of the left kidney, associated with dystopia of the right; removal of the misplaced organ with failure to recognize the absence of the other kidney was followed by the inevitable. In Rolleston's case, a 12 year old child, the right kidney was absent but the vesical half of the ureter was present.

Unilateral absence of the kidney is frequently associated with other anomalies, and especially with those of the genital tract. This is not surprising, in view of the close embryologic relation of the two systems. The genital anomalies are important because they may give the clew which leads to the discovery of the renal anomaly. In Ballowitz' tabulation the condition of the genital system was mentioned in 103 cases and was given as normal in 30 and abnormal in 73. Of the latter, 28 were males, 41 females, and in four the sex was not stated. The greater frequency in females may be due to the greater ease of the detection of uterine anomalies. The genital anomaly is usually on the same side as the renal defect, and usually occurs in the efferent system and not in the gonads. In females, uterus unicornis is the most frequent anomaly. In males, the epididymis may be rudimentary or absent; the vas, seminal vesicle and ejaculatory duct may be absent; the prostatic lobe may be rudimentary. Since the renal vascular supply is not developed until the permanent position of the kidney is attained, renal vessels are absent when the kidney is absent. Although the adrenal is not developed from the urogenital anlage, its close proximity to the kidney during fetal life may bring it within the influence of the factors which lead to absence of the kidney. Ballowitz found the condition of the adrenal noted in 111 cases; in 31 of these it was absent. The right adrenal was absent in Rolleston's case.

Anomalies of Form and Size.—Hypoplasia of the Kidney.—In unilateral hypoplasia, as compared with unilateral absence of the kidney, a rudimentary kidney has been formed but is strikingly smaller than normal. It usually has a ureter, which may be fibrous and without a lumen. Elements derived from the renal mesenchyme, i.e., glomeruli and tubules, are present. The small kidney is supplied with blood-vessels which, in their course and distribution, are usually normal. Everything indicates, therefore, that the renal bud was normally formed and that the development of the kidney continued to the stage of union of mesenchymal mass with renal bud, with the development of normal vascular relations and the attainment of the normal position of the kidney. Whether the further development of the kid-

ney ceases at this stage, because of the loss of a hypothetic growth stimulus, or whether the kidney continues further in its development and then undergoes regressive or atrophic changes cannot be determined. Of the various names which have been applied to the condition, some, like hypoplasia and hypogenesis, indicate defective or arrested development; others, like congenital unilateral atrophy, relative atrophy, unilateral hypogenetic nephritis, implicate regressive or inflammatory processes.

Microscopically the hypoplastic kidney has many points of similarity with the small contracted kidney of chronic interstitial nephritis. The glomeruli are small and often fibrotic. The tubules are atrophic. The parenchymatous elements lie more widely separated than normal in a cellular stroma which is often rich in small round cells. Regenerative phenomena are sometimes seen in the tubular epithelium. The walls of the arteries are thick. These changes have been interpreted as evidences of an interstitial inflammatory process which leads to atrophy of the kidney. That inflammation is actually the primary process may be doubted. Simpson, who has reported a case in a 13 month old girl, concludes that the small round cells in the interstitial tissue are lymphocytes and, therefore, are an indication of inflammation. That these cells are not undifferentiated mesenchymal elements, masses of which may remain undeveloped in congenital renal tumors, has not been excluded. Fibrosis of glomeruli and atrophy of tubules may be secondary to a simple failure of the kidney to develop normally.

If unilateral hypoplasia is primarily an inflammatory or regressive process, some reason must be adduced to explain the involvement of only one kidney. This is attempted by Coplin, who, from a study of nine cases, considers hypogenesis of the renal arterial system the basis of the renal anomaly. In a kidney whose arteries are under-developed the blood supply might be inadequate for proper nutrition, resulting in failure of the kidney to develop further. Another possibility considered by Coplin is that a kidney with such a congenitally defective vascular system might be more susceptible to toxic and other harmful agencies, which are able to set up an inflammatory process, although they would not have this effect in a normal kidney. It is true that the arteries of hypoplastic kidneys have thick walls and relatively small lumens, but again it is impossible to say that this is the primary condition. If the arterial system is laid down normally and the parenchyma is hypoplastic and does not function, absence of a normal volume of circulating blood in the arteries would cause just such a condition of apparent arterial thickening as occurs. The exact nature of the process which leads to unilateral hypoplasia must be considered as still undetermined.

Hydronephrosis may occur in a hypoplastic kidney (Marion). In the case reported by Beracqua calyces, pelvis, pyramids, and the upper third of the ureter were absent. The renal parenchyma was represented by a small mass of tissue made up of rudimentary tubules and

a few glomeruli; the condition was interpreted as the result of the separation of the lower and upper portions of the renal anlage after their primary union had occurred, the separation being followed by failure of further development. In Papin and Verliac's case, the solid ureter from the hypoplastic left kidney ended in the seminal vesicle. Hypoplasia of the kidney is said to be less frequent than unilateral absence. In Braasch's series of 38 congenital anomalies, there were five cases of hypoplasia to six of unilateral absence.

Lobulation of the Kidney.—During the early embryonic stage of the kidney multiple lobules or renculi are formed by the continued branching and subdivision of the primary calyces, the terminal divisions being covered by the renal mesenchyme. In the normal kidney, fusion occurs between the lobules, the lines of fusion resulting in the columns of Bertini. If normal fusion does not occur or is not complete, due to early covering by the capsule, fetal lobulation of varying degree persists. Lesser degrees, in which the surface of the kidney is subdivided by a number of shallow grooves or fissures, are not uncommon.

Discoid Kidney.—The shape of the kidney may be globular, discoid or spleen-like. Such anomalies of shape have been ascribed to alcoholism; they have been found in young children and fetuses, as well as in adults, and alcohol can be excluded as a factor. The condition is apparently the result of interference with the normal rotation of the kidney on its long axis during the early fetal period, or to excessive rotation. In cases of the first kind the hilum is anterior and the kidney retains its fetal, discoid shape. If the rotation is extreme, the hilum is situated posteriorly and the anterior or ventral surface becomes rounded.

Hypertrophy of the Kidney.—Increase in the size of the kidney may be associated with congenital unilateral absence or hypoplasia of its mate. Such enlargement is to be considered compensatory. A maldevelopment termed by Schenkl "fetal giant kidney" will be considered under Congenital Cystic Kidney.

Anomalies of Position.—The permanent position of the kidney may be an abnormal one. The abnormality may be acquired or congenital; in the first group the renal arteries usually have a normal origin from the aorta. In the congenital malpositions, which alone will be considered further, the vascular supply is often abnormal. The kidney may be displaced in a vertical or in a horizontal direction; the anomaly may be unilateral or bilateral, the latter, however, being infrequent.

Vertical Dystopia.—Theoretically the kidney may have a position either above or below the normal. A position higher than normal is extremely rare. Downward displacement of one kidney, the other being in normal position, is the most frequent form of renal dystopia. The left kidney is more often misplaced than the right; Strube collected 47 cases of left-sided dystopia as compared with 16 cases of the right side. Downward dystopia of one kidney may be associated with absence of the other. Ballowitz found this condition in three of

the 213 cases tabulated by him and Strube has reported two cases. Usually the misplaced kidney lies at the brim of the pelvis or even entirely within the pelvis. Downward displacement of both kidneys is rare. Strube found only four recorded cases; Bryan was able to find 18 cases confirmed by autopsy. Tattersall has recently reported an additional case, an 18 year old boy who died in uremic coma; both kidneys, which lay on the alae of the sacrum, were very small and showed a marked degree of chronic interstitial nephritis; the bladder and both ureters were greatly dilated but without any determinable obstruction. Walther has reported a case in which the diagnosis of bilateral dystopia was made by roentgenography.

Horizontal Dystopia.—In this condition, also termed crossed dystopia, one kidney is in the normal position. The misplaced one lies on the same side as the normal one and usually below the latter, but the ureter opens normally into the bladder. Crossed dystopia without fusion is very rare; Strube was able to find only one recorded case. The anomaly recently reported by Burrows may be an additional example. Vagina, uterus, broad ligament, right tube, right ovary and right kidney were absent. The left ovary and the fimbriated portion of the left tube were present. In the left lumbar region was a hypoplastic kidney. In the left pelvis was a globular, lobulated kidney. These findings were ascertained at operation and the ureteral relations were not determined. It is impossible to decide, therefore, whether this is an example of complete absence of the right kidney with double left kidney, or of hypoplasia of the left kidney with downward vertical and crossed dystopia of the right kidney; the latter appears to be the more probable.

Girard classifies the congenital dystopias as follows: (1) Dystopia of one kidney, the other being in normal position. (2) Dystopia of one kidney with absence of the other. (3) Bilateral dystopia. Each of these groups is further subdivided according as the dystopia is homolateral or crossed, and according to the level of the kidney (low lumbar, iliac, pelvic). His tabulation of reported cases includes under Group 1 114 examples of left-sided and 72 of right-sided homolateral downward dystopia, 12 of crossed dystopia, and 2 of upward displacement of the left kidney. In Group 2 he places 12 cases of homolateral and 3 of crossed dystopia. Under Group 3 he includes 21 homolateral cases, and 2 cases of crossed bilateral dystopia, the latter determined by operative and clinical findings but not verified by autopsy.

Abnormal position of the kidney is due to interference with the normal migration of the organ during the early fetal period. The actual mechanical factor which interferes with migration cannot be determined in every case, but lack of room and abnormal crowding during the early developmental stage would seem to be the most generally applicable. Bryan believes that as the kidney moves cephalad it attains a new, temporary blood supply at each higher level, those ves-

sels which were developed at the preceding lower level disappearing. If the temporary vessels do not disappear the kidney remains stationary, anchored by the abnormal vessels which become permanent. This explanation is a simple one and fits in with the abnormal vascular supply of the dystopic kidney. But according to the work of Pohlman and others, the kidney does not receive its vascular supply until it reaches its permanent position. The abnormal vascularization of the misplaced kidney would, therefore, be the result rather than the cause of the anomaly of position.

The vascular supply of the misplaced kidney may be quite variable and appears to depend upon the position finally reached. If the organ is situated low in the pelvis the arteries may arise from the common iliacs; if somewhat higher, the arteries spring directly from the aorta at or some distance above the bifurcation. There are usually several main arterial branches, although in the case of pelvic kidney reported by Dufoir and Thiers the ectopic organ was supplied by a single artery which arose at the site of the middle sacral artery, the latter vessel being absent. Anitschkow described four types of vascular supply: (1) A single renal artery arising from the aorta at the region of the bifurcation; (2) in addition to an aortic branch arising at the bifurcation, there may be from one to five other branches which arise directly from the aorta at a somewhat higher level; (3) the arteries come both from the aorta and from the common iliacs or other larger abdominal or pelvic arteries; (4) there are no aortic branches, all the arteries coming from the abdominal or pelvic branches of the aorta. The veins usually accompany the arteries.

As previously noted, interference with the ascent of the kidney is usually associated with incomplete rotation in the long axis of the kidney. As a result, the pelvis of the dystopic kidney is usually anterior and the kidney does not assume its normal shape; it is discoid or rounded.

Dystopia of the kidney is associated with genital anomalies in almost as large a proportion of cases as is absence of a kidney. In Strube's third case the right testis was absent; a palpable mass over the sacral promontory was held to be a sarcomatous retained testicle, but was found at operation to be an ectopic kidney, removal of which was followed by anuria and death; the other kidney was found to be absent at autopsy. Heiner recorded 35 cases of renal dystopia with genital anomaly; of these 25 were females and 10 were males.

Congenital misplacement of the kidney need not be associated with any symptoms which can be ascribed to the kidney, and Strube claims that the ectopic kidney is no more frequently subject to pathologic conditions than is the normal organ. In Thomas' case there were repeated renal crises with constant pain; the kidney was situated in the left iliac fossa; the vagina was rudimentary and no internal genitalia could be palpated. In the case of horizontal dystopia reported by Lahey and Paris and which had been mistaken for a mesenteric cyst,

there were recurrent attacks of abdominal pain. Crises and pain, when present, may be the result of abnormal mobility of the misplaced organ or of abnormality in the course of the ureter. Whether a movable kidney in any given case is an example of congenital dystopia or is an acquired condition must be determined by the vascular relations. The misplaced organ may be palpable.

Fusion Anomalies.—Horseshoe Kidney.—Fusion of the lower poles of the kidneys, with no or only slight downward displacement, occurs in from 0.7 per cent. of autopsies (Taylor) to 1.4 per cent. (Felty). The result of the fusion is the typical horseshoe kidney, with the concavity upward. The pelves may be more ventrally situated than normal and may be poorly developed, the ureters arising by a fusion of calyces. The ureters open normally into the bladder, but anomalies in their course may pre-dispose to hydronephrosis. Supplementary anomalous vessels, arising directly from the aorta below the normal renal arteries, are not unusual (Jéprémoff). The normal arteries supply the upper portions, the anomalous ones the isthmus. The latter may be composed of connective tissue or of parenchyma. If there are no pathologic changes, the horseshoe kidney may lead to no symptoms. In some cases abdominal pain and indefinite gastro-intestinal disturbances are present. The isthmus, where it lies over the vertebral column, may be palpable. Hydronephrosis, lithiasis and pyonephrosis appear to occur more frequently than in the normal kidney. Botez records the occurrence of sarcoma of a horseshoe kidney in a boy of four years. Pre-operative diagnosis favors conservative measures when only a portion of the fused kidney is involved.

Lateral Fusion without Dystopia.—A much rarer form of anomaly is that in which the fusion has occurred along the greater portion of the median borders of the two kidneys, resulting in a discoid mass whose pelvic portion lies in the mid-line. From the compound ventral pelvis the two ureters run to their normal openings into the bladder.

Fusion with Dystopia.—The form of fusion anomaly in which a kidney in normal position is fused with its mate, the latter being drawn partly or completely across the mid-line, ranks next in frequency to horseshoe kidney. In this condition the fusion is associated with crossed dystopia; often a varying degree of vertical dystopia is also present in the misplaced kidney. More often the left kidney is misplaced, the right being in normal position. If the fusion has occurred by the lower poles, the misplaced kidney lies at a lower level than the other and transversely across the mid-line (Fig. 177). In other cases there is a greater degree of lateral dystopia and less vertical dystopia, the posterior surface of the misplaced kidney being completely fused with the anterior surface of its mate. The result is a large, globular or "hog backed" kidney with a double pelvis from which two ureters are given off; one of these crosses the mid-line and empties into the bladder on the side opposite the fused kidney. It is this normal ureteral relation which differentiates such a fusion anomaly from a reduplication

anomaly with true absence of the opposite kidney. Examples of this type are reported by Hill, Felty, and Huntington. The last named writer describes and illustrates a group of cases which show all the gradations of fusion anomaly from the typical horseshoe kidney with normal position to the complete fusion of the two organs on one side of the body.

In the 25 recorded cases tabulated by McMurrich (quoted by Huntington), the right kidney was misplaced in 40 per cent., the left in 60 per cent.; of 23 cases, 78 per cent. were males and 22 per cent. females. The variations in that portion of the venous system which lies below the mouths of the normal renal veins are considered in detail by Huntington and are derived from the post-cardinal veins of the fetus.

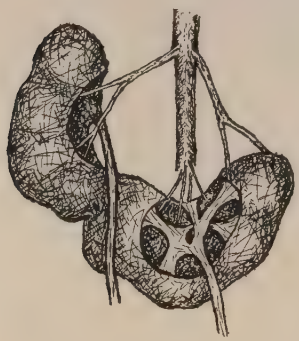

Fig. 177.—Fusion dystopia, human fullterm fetus (two-thirds size).

The misplaced portion of a fused kidney has such anomalies of arterial supply as have already been considered above under anomalies of position. Dystopia with fusion may be associated with the same genital anomalies as occur in dystopia without fusion or in absence of the kidney. In the case from which Fig. 177 comes, the left testis, epididmyis and vas were absent, the left half of the scrotum was rudimentary, and the penis was absent.

Fusion of the kidney, with or without dystopia, is probably due to the same mechanical factors of crowding and lack of room which act to produce dystopia alone. According to Pohlman, the mesial surfaces of the renal buds in the human embryo are only 50 microns apart when the buds are first formed. Whether fusion occurs depends upon the proximity of the embryonic kidneys to each other at the time the mechanical factor is active. Interference with the ascent of one kidney, the migration of the other occurring normally, appears to explain those cases in which the misplaced kidney is dragged partly across the midline by its mate. Complete fusion of the two kidneys, the fused mass attaining the normal position of one of the kidneys, is due to early fusion without interference with ascent.

Vascular Anomalies.—Variations in vascular distribution associated with malposition of the kidney have already been mentioned. The normal kidney may have an anomalous arterial supply, which is sometimes of clinical importance. The most recent and thorough study of the variations in the vascular supply of the normal kidney is that of Eisendrath. The results obtained in this study of 218 kidneys may be added to those previously obtained by Eisendrath and Straus in a study of 200 kidneys. In 71.1 per cent. the renal arteries were normal; in 4.2 per cent. an accessory renal artery arising directly from the aorta ran to the upper pole of the kidney; in 8.0 per cent. an acces-

sory artery ran directly from the aorta to the lower pole; in 0.48 per cent. an artery to the lower pole was derived from the iliac arteries; in 0.24 per cent. the renal artery itself gave off a branch to the lower pole.

More important from the clinical standpoint are those anomalous vessels which give rise to hydronephrosis by compressing the ureter. Abnormal vessels which cause hydronephrosis are usually such as compress the upper part of the ureter, at or near its junction with the pelvis. As a rule they are vessels which go to the lower pole of the kidney or to the inferior margin of the hilum; they may pass either anterior or posterior to the ureter. Of nine surgically treated cases of hydronephrosis reported by Borelius, five were due to anomalous vessels. In the Mayo statistics 20 of 28 cases of hydronephrosis were due to abnormal vessels; mere ligation and section of the vessels was sufficient to relieve the condition in 13 of these. Borelius believes that abnormal mobility or descent of the kidney is usually an important additional factor in hydronephrosis due to abnormal vessels. Klukow, in 1912, was able to collect 57 cases of hydronephrosis due to abnormal vessels. Early diagnosis is important because conservative operative measures may result in the saving of the kidney.

Ureteral Anomalies.—In the literature there are scattered references to anomalies of the ureter other than those already considered. A frequent result of such abnormalities is hydronephrosis; so-called congenital hydronephrosis, when it is a true hydronephrosis, is almost invariably the result of some anomaly in the ureter which interferes with the urinary outflow. Pepere has reported an unusual case of multiple diverticula of both ureters in a child. Multiple dendritic branchings of the ureter had led to the formation of diverticula, some of which were pendant and others interstitial. The walls of the diverticula had the same structure as the wall of the ureter. Filling of the diverticula obstructed the ureters and caused bilateral hydronephrosis and death from anuria. Congenital stricture, due to valve-like folds into the lumen of the ureter, are not rare. During the embryologic period the mucosa of the ureter is normally thrown into transverse folds; most of these begin to disappear at about the fourth month, but some may still be present in about 5 per cent. of newborn infants (Jeanbrau). When such folds persist and lead to obstruction they are usually situated at the junction of the ureter with the pelvis, in the iliac segment, or in the intramural portion. Congenital atresia of the ureteral meatus occurs. Cases in infancy and childhood have been reported by Anscherlik, Furnival, Bottomley and Johnson; the subject of ureterocele due to narrowing of the meatus is reviewed by Lavendera, who described four cases in adults. Complete occlusion of the meatus of accessory ureters has already been mentioned. Michailow described a case of hydronephrosis in which the obstruction was due to a congenital, wart-like projection from the ureter into the renal pelvis. Cystic or saccular dilation of the ureter, not due to obstruction, may occur. Marion reported a case of multiple dilata-

tions of the left ureter, without obstruction; each ureter opened into the bladder at the summit of a hemispherical dilatation. In Tattersall's case of bilateral vertical dystopia with chronic interstitial nephritis, the ureters and the bladder showed a marked degree of "idiopathic" dilatation. Two cases of idiopathic, so-called congenital dilatation of the ureters (Fig. 178) in young children have recently been seen in the Sarah Morris Hospital for children. In neither of these cases was there any obstruction; both were complicated by pyelitis.

FIG. 178.—Idiopathic (congenital?) dilatation of ureters.

CONGENITAL CYSTIC KIDNEY

Cystic kidney is one of the less infrequent congenital anomalies of the kidney. It is a condition of some clinical importance, because it may interfere with the birth of the child or because of its later effect upon the individual. It is of great pathologic interest, because of the diversity of opinion which has existed as to its genesis and because of the number of eminent pathologists who have made contributions to the controversy.

Pathology.—In a typical example the kidney is enlarged and is studded with thin-walled cysts which are filled with clear fluid of urinary character. The size of the cysts varies with the degree to which the condition is developed at birth; in later life the size of the cysts is probably also partly dependent upon the degree to which secretion into the cysts continues. The best examples for study are

those in which at birth the organ is only moderately enlarged; in these the cysts are from one to a few millimeters in diameter, and the renal tissue has a honeycombed appearance somewhat suggestive of a colloid thyroid gland. From such cases there are all gradations to that condition in which the kidney is so greatly enlarged as to cause visible prominence of the abdomen, the individual cysts reaching a size several centimeters in diameter. Unless there has been inflammatory thickening of the capsule, the surface cysts are so thin walled as to be almost transparent. The surface is irregular because of the projection

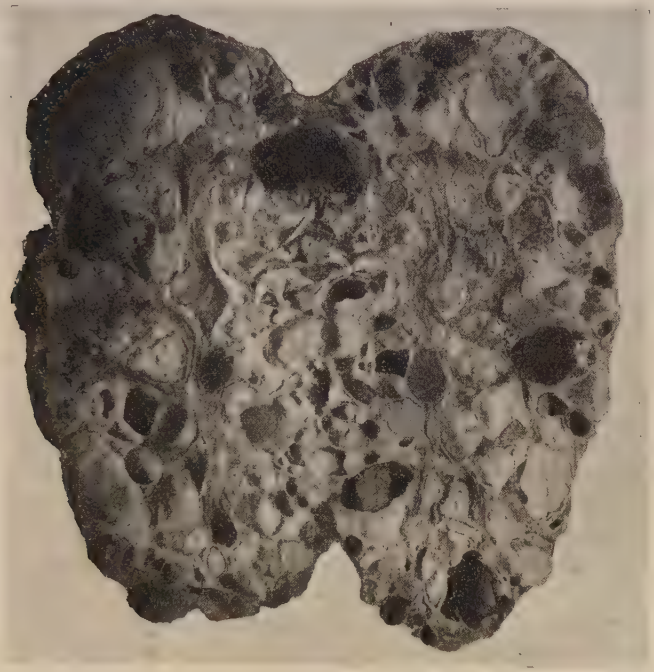

FIG. 179.—Longitudinal gross section of congenital cystic kidney.

of the cysts above the general surface level. On section the cysts are present throughout the kidney, (Fig 179) being usually more numerous in the cortical than in the medullary portion. The amount of tissue between the cysts varies; it may be reduced to a minimum or it may be several millimeters thick.

The microscopic picture may be quite variable, a fact which has made for difficulty in the interpretation of the nature of the condition and has helped to cause diversity of opinion as to its genesis. In the small cystic variety which one occasionally encounters at birth, the spaces are rounded or elongated, and they are lined by a single layer of cuboidal epithelium, somewhat lower than that of the convoluted

tubules but of the same general character. The capsules of the glomeruli are distended by fluid. Normal tubules may be present in the tissue between the cysts. In more marked examples with larger cysts the epithelium of the latter may be greatly flattened and atrophic and may finally disappear completely. In other cysts the epithelium may be hyperplastic and may form papillary ingrowths into the cyst lumen. The intercystic tissue may be reduced to a minimum which is incompatible with function, or it may contain secreting tubules and glomeruli in sufficient numbers to maintain life. Groups and masses of small round cells are often present. Some of these may be lymphocytes, whose presence is evidence of a low grade of inflammatory reaction. More often they are islands of undifferentiated, fetal, parenchymatous tissue. Smooth muscle and fibrous tissue in varying amounts may be present in the intercystic stroma, and small islands of cartilage have been described. The failure of development of parenchymatous elements and the presence of heterologous tissues have some bearing upon the interpretation of the process.

Congenital cystic kidney is usually bilateral and polycystic. More rarely there may occur in the kidney single cysts of a size larger than those which may develop as the result of simple occlusion of a tubule. Whether such a condition is congenital and belongs in the same category as the polycystic condition is difficult to determine. According to Vogel, who considers such single cysts congenital in origin, they arise in the cortex and are usually situated at the lower pole of the kidney.

The cystic condition of the kidney may be associated with cysts in other organs, especially the liver. Herxheimer was able to collect 50 cases in which both the kidneys and the liver were cystic. Less frequently cysts may occur in other organs, pancreas, choroid plexus, cerebellum, lung, uterus, spleen, etc. Associated developmental anomalies, as hydrocephalus, encephalocele, polydactyly, club foot, cleft-plate, harelip, and genital defects, are not infrequent.

Frequency.—A point of some importance is the familial occurrence of polycystic kidney, which has been noted by a number of observers. One of Busse's cases was the thirteenth child of a women aged 41 years; of the other children, the first, fourth, seventh and tenth also had cystic kidneys. In the family reported by Wobus this familial tendency is even more marked. The first three children had markedly cystic kidneys; the fourth child was living and was reported as probably having the condition; the fifth pregnancy ended in abortion at four months and the fetus was not examined; the sixth pregnancy resulted in a full-term, stillborn child with polycystic kidneys; the seventh child was apparently normal. More than one generation may be affected.

Bircher, in a paper in which the literature is carefully covered, gives the following age relations from a tabulation of 239 cases by Küster: Born dead or dying shortly after birth, 59; death during the first year, 10; 1 to 5 years, 6; 5 to 10 years, 1; 10 to 20 years, 4; 20 to

30 years, 22; 30 to 40 years, 24; 40 to 50 years, 53; 50 to 60 years, 41; 60 to 70 years, 10; 70 to 80 years, 6; 80 to 90 years, 3. Such a tabulation of the time at which death occurred shows, first, that in a fairly large proportion of cases (28.8 per cent.) the lesion is so marked as to lead to death during the intra-uterine period or during the first year after birth; secondly, that in cases in which the condition is less marked, the life of the individual is not greatly influenced until the age period of 20 to 61 years, when greater work demands are thrown upon the kidney and the small amount of parenchymatous tissue present becomes insufficient for adequate renal function; 58.5 per cent. of the cases fall into this group; thirdly, in a small group of cases (7.9 per cent.), the cystic condition causes no appreciable shortening of life. The two sexes were found to be equally affected by Küster in 224 cases. Of an equal number of cases tabulated by Sieber (as quoted by Bircher), 58 per cent. were females, 42 per cent. males; but in 70 operated cases in this group there where 61 females to 10 males; of the cases not subjected to operation, 56 per cent. were males and 44 per cent. were females. Sex, therefore, does not appear to have appreciable bearing on the condition. Lund estimates that both kidneys are involved in 98 per cent. of cases. In nine unilateral cases, the left kidney was involved six times, the right three times (Bircher). In the majority of the bilateral cases the left kidney is more markedly involved than the right or gives evidence of involvement earlier.

Pathogenesis.—The first theory of the pathogenesis of polycystic kidney to receive acceptance was that of Virchow. He attached great importance to plugging by uric acid of the terminal portions of the urinary tubules in the papillæ of the kidney. He believed that occlusion of the tubules during fetal life by such uric acid infarcts, as he termed them, could lead to retention within the tubules and that the retention would result in the cyst formation characteristic of the condition under consideration. Later it became necessary for him to modify his view somewhat, in that he ascribed greater importance to a fetal interstitial papillitis as the cause of tubular occlusion than to uric acid infarction. Virchow's conception, that chronic inflammation of the renal papillæ, occurring especially during the fetal period, leads to atresia of the tubules, to which cystic degeneration of the kidney through retention is secondary, received general acceptance for a time. But cases were described in which no evidence of such an inflammatory process could be found; and, on the other hand, chronic inflammation of the adult kidney, with occlusion of tubules but without the formation of a cystic condition in any way comparable with the congenital form, is a frequently encountered process. Experimental occlusion of the tubules in the medullary or papillary portion of the kidney causes only small retention cysts. Those who, like Phillipsohn, still held to Virchow's view in spite of the objections which had been raised, found it necessary to suppose that the polycystic kidney of adults has a genesis different from that of the congenital variety.

Brigidi and Severi (quoted by Busse) in 1880 applied the term "cistomi dei reni" to the cystic kidney, and Chotinsky (1883) emphasized the proliferative epithelial changes which may be present, especially in the cystic kidney of adults. Hanau (1890) described aplasia of the medullary and papillary portion of the cystic kidney; this aplastic condition, which he considered to be the basis of cyst formation, he held to be a developmental failure. Three fundamentally different views of the origin of polycystic kidney had thus been developed; the inflammatory theory, the neoplastic theory, and the developmental anomaly theory. Since 1890 the controversy has continued, but it has been chiefly between those who maintain that cystic kidney is a developmental anomaly and those who consider it a neoplastic condition; there has been little support for the older inflammatory theory, which may well be dropped from further consideration.

Nauwerck and Hufschmidt held the cystic condition to be the result of epithelial proliferation, evidences of which were still present in the specimen studied by them as papillary epithelial ingrowths into the cysts. The cysts were formed in part by colloid degeneration of the new formed epithelium, in part by transudation from neighboring vessels. They considered the condition a multilocular cystoma or adenocystoma, in which the cysts are derived from neoplastic epithelial structures and not from the original tubules. v. Kahlden also accepted the neoplastic theory, but believed that retention, following epithelial proliferation, was the important factor in bringing about the cystic condition. In a later publication the congenital character of cystic kidney was emphasized, because of the occurrence of large amounts of fibrous tissue or of islands of mucoid tissue, and he looked upon the condition as a congenital myxofibroadenocystoma. Borst likewise accepted the neoplastic theory, but attached importance to an anomaly in development which causes a disturbance of the normal relations of stroma and epithelium; the epithelial proliferation and cyst formation are secondary to this congenitally disturbed relation.

The neoplastic theory is accepted also by Berner and by Vorpahl. Staemmler, a pupil of Nauwerck, is the most recent adherent of this view, but he, like Borst, takes an intermediate stand and admits that maldevelopment is an essential part of the process. He holds the cystic condition to be of the nature of a primary tumor in a malformed kidney but not a necessary sequence of the maldevelopment.

The belief that polycystic kidney is the result of a developmental anomaly pure and simple and that it has no relation to tumor formation received its strongest support from Ribbert. His conclusions were based not only upon a study of examples of cystic kidney, but also upon an embryologic study of the development of the kidney. Among the embryologists there had been controversy as to whether the kidney is derived from a single or a double anlage. Ribbert, from his own embryologic studies on the guinea pig, accepted the dual origin of the kidney, a view which is supported by the researches of Pohlman on the

human kidney and of Schreiner and others in lower animals. According to this present conception of the origin of the kidney, the renal bud, an outgrowth of the Wolffian body, gives rise to the ureter, pelvis, calyces, and collecting tubules of the medulla. The actively secreting portion of the kidney, composed of the convoluted tubules and the glomeruli, which make up the cortex and the columns of Bertini, are derived from the renal mesenchyme, which at an early stage covers the free cephalic portion of the renal bud and fuses with the latter. This conception of renal development greatly simplifies the question of the origin and nature of polycystic kidney. If the cortical tubules, formed from a distinct upper renal segment, must unite with the collecting tubules, formed from a separate lower segment, a failure of the normal fusion to occur is to be expected in a certain proportion of cases, just as fusion failures lead to anomalies in the region of the face, of the central nervous system, and elsewhere. The cystic dilatation of the tubules is the result of retention in the occluded tubules, but the retention and dilatation must probably have their beginning during the fetal period, since occlusion in the post-natal period apparently does not lead to a very great degree of distention. The papillary epithelial ingrowths into the cysts are the result of a secondary proliferative reaction on the part of the epithelium.

There are several observations which indicate that the developmental error may consist of more than a mere failure of fusion of cortical and medullary tubules. Meyer has reported a case in which the non-cystic kidney of a girl of nine weeks contained multiple small pale areas separated by normal renal tissue. These areas were cellular, being composed of cells like those in the normal convoluted tubules, but no tubule formation had occurred. Meyer interprets the condition as a failure or inhibition of development of the tubules in the abnormal areas. Schenkl studied a condition which he termed fetal giant kidney. From his discussion it is apparent that he was dealing chiefly with typical polycystic kidney. But in two reported human cases and in a calf studied by him, the kidneys were greatly enlarged and not cystic. The medulla could not be distinguished. Microscopically glomeruli were present, but most of the tissue was solid and cellular, with only slight tubule formation. He considers the condition due to failure of development of tubules, the tissue persisting in a hyperplastic, undifferentiated form. One of the most important studies is that of Busse. He called attention to the relatively large amount of interstitial stroma which may be present in the medulla and which surrounds the individual medullary tubules or groups of tubules. This condition has been frequently described and was considered evidence of fetal interstitial inflammation by those who upheld the inflammatory theory of cystic kidney. Busse, however, is convinced that the tissue is in large part undifferentiated smooth muscle and that its presence is not the result of inflammation. Study of normally developing human kidneys showed that large amounts of smooth

muscle are present in the medulla of the kidney, being derived from the muscle of the ureter and pelvis. In the fetal kidney the smooth muscle surrounds the medullary tubules in the way that is so characteristic of cystic kidney. As the tubules multiply the muscle disappears. In the polycystic kidney there is cessation of development during this stage of high muscle content. An inadequate number of collecting tubules is formed, so that some of the cortical tubules must fail to find an outlet. The intracystic papillary ingrowths, seen by so many, Busse believes to be remnants of vascular tufts in cystically dilated glomeruli. The islands of small round cells so frequently seen in cystic kidneys are areas of undifferentiated fetal renal tissue, which has not gone on to the formation of tubules. This writer, therefore, conceives the polycystic kidney to be the result of a developmental error which is characterized by failure of normal differentiation and development within the kidney; it is difficult to find a satisfactory translation for the word "Hemmungsbildung," used for errors of this type.

The theory that polycystic kidney is the result of a developmental anomaly appears to be the most acceptable. The degree to which the condition develops and the amount of functioning kidney tissue which is present in any given case will depend upon the extent to which normal differentiation occurs during the fetal period and upon the number of cortical tubules which are able to find an outlet to the pelvis. In this connection it is interesting to note that v. Meyenberg explains the congenital cystic condition of the liver, which may be associated with polycystic kidney, upon the basis of a developmental error analogous to that which causes the latter condition; namely, a failure of union of intralobular bile ducts (bile ducts of the first order), which are formed after the parenchyma has begun to differentiate, with the interlobular ducts (bile ducts of the second order), which are formed earlier by repeated division of the primary hepatic evagination given off from the duodenum.

Symptoms.—Polycystic kidney may not be associated with any symptoms which direct attention to the renal condition. When symptoms are present they depend, in part, upon a deficient amount of secreting kidney tissue; in part, upon such a size of the organ that the latter is palpable or causes visible abdominal enlargement; in part, upon complications which may be added to the cystic condition. So long as the amount of secreting renal parenchyma between the cysts is adequate for the needs of the body, the urine may be normal. If renal insufficiency is present because the parenchyma is inadequate from the beginning or if the insufficiency develops later because of greater demands which are made upon the parenchyma present or because part of the tissue becomes involved in chronic inflammation, then the symptoms and course of the disease may be quite identical with those of chronic interstitial nephritis. The urine is increased in quantity, and is of low specific gravity. The reaction of the urine

is usually acid. Albumin may be absent, or may be present as a trace as in interstitial nephritis. The urine may contain a few hyalin casts. Radially and concentrically striated colloid globular bodies may occur in the urine and have been held by some to be characteristic of polycystic kidney. If suppuration of a cyst occurs, the urine may contain pus cells. Hematuria occurs in about one-fifth of the cases; the amount of blood varies from quantities so small that they are detected only microscopically to quantities so large that coagulation may occur. In the former case the hemorrhage is supposed to be due to diapedesis; in the latter case to rupture of vessels. As the secreting renal tissue becomes progressively more insufficient, nausea, vomiting, headache, diarrhea, coma, and the other manifestations of uremia may develop. In such cases the blood shows the retention of waste products found in interstitial nephritis.

The cystic kidney may become palpable, due to progressive enlargement of the cysts. Or it may be already so large at birth as to interfere with delivery. Fluctuation is not usually obtained; the mass may feel nodular. The weight of the organ may lead to pain in the lumbar region, or it may cause the kidney to become movable, when hydronephrosis may occur as a complication. The pain may be colicky and may be followed by hematuria. Infection leads to suppuration in about 10 per cent. of the cases; the urinary contents of the cysts become transformed into pus. The suppurating cyst may rupture into the renal pelvis, causing pyonephrosis; or it may break internally, causing perinephritic abscess; rupture into the intestine has been described. There may be hemorrhage into other organs (apoplexy, hemorrhagic retinitis, etc.) as in chronic nephritis.

Treatment.—Because of the almost constant involvement of both kidneys, nephrectomy is associated with a high mortality. It should be done only in cases of the extremest necessity, and only then when tests indicate that the other kidney is capable of adequate function. Indications for operation are hydronephrosis due to mobility or to pressure upon the pelvis or ureter by one of the cysts; pain due to increasing weight of the tumor; suppuration; hemorrhage; pressure of the tumor upon other organs; anuria, due to pressure upon the secreting tissue by increase in the size of the cysts. When operation becomes necessary for any of the causes mentioned it should be as conservative as possible. In most cases simple incision with evacuation of the cysts opened by the incision is all that can be done. If infection is present, incision must be followed by drainage. Drainage of uninfected cysts is to be avoided, because of the possibility of secondary infection. Decapsulation has been tried, but the results are not so good as those of simple incision.

TUMORS OF THE KIDNEY

The kidney is one of the more frequent sites of tumor formation in children. Porter and Carter, from D'Espine and Piso's tabulation

of 396 cases, give the incidence as 20 per cent., the kidney being second to the eye and orbit with 52 per cent. This relative frequency of tumors of the kidney is due chiefly to the congenital mixed tumor of this organ. Other forms of tumor occur in the kidney during the early years of life in small numbers. How frequent such other forms are is not easy to determine from the literature, because some of the reported cases of sarcoma and carcinoma are undoubtedly mixed tumors. Thus, Porter and Carter, in San Francisco, were able to examine the records of 11 cases of kidney tumor in children under seven years of age. Excluding two cases of hydronephrosis, they report four sarcomas, three carcinomas, and two unclassified malignant tumors. The case which they described in detail they call a round- cell sarcoma, but the photomicrographs make it probable that this was a mixed tumor; the other tumors called sarcoma and carcinoma were also probably mixed tumors. The same is true of the tumors called sarcoma by Monti, who collected nine cases of primary sarcoma occurring between the ages of seven months and six years. These were spindle-cell tumors in which striated muscle was present.

Small nodules composed of fibrous tissue or of fibrous tissue and smooth muscle may occur in the medulla. These, according to Busse, are remnants of fetal interstitial tissue which failed to disappear in the differentiation of the kidney. Small masses of subcapsular fat may be carried down into the tissue when the renculi fuse; such lipomas may retain the mucoid character of fetal adipose tissue. Adenomas may occur in the cortex; they are probably derived from undifferentiated rests of fetal renal parenchyma. Small yellowish nodules composed of misplaced adrenal cortex are not infrequently seen in the renal cortex. Hemangiomas of the kidney have been described.

Most of the malignant tumors which involve the kidney during childhood are primary. Usener has reported a spindle-cell sarcoma of the kidney of a girl four and one-half years old; there were metastases in the retro-peritoneal tissue and in one of the ribs. Rossi has described a round-cell sarcoma weighing 600 gm. in the kidney of a child two years old; the child was living and well eight years after nephrectomy. Grego's case of round-cell sarcoma of the kidney of an infant aged 18 months occupied most of the left half of the abdomen. Kästner has very recently described a spindle-cell sarcoma of the kidney of a seven months' fetus. A peculiar and unusual condition of diffuse bilateral round-cell sarcomatosis of the kidney in an adult has been reported by Fürstenberg and Büchmann, who considered the process a primary bilateral renal tumor. v. Werdt described a similar condition in an 11 year old boy, but in this case there was a mediastinal tumor of similar character, to which the renal involvement was considered secondary. Wehland believed his case of this type, in a child aged ten months, to be a primary involvement of the kidney, although tumors were also present in the skull, liver, ribs, heart muscle and brain. In Schwers and Wagner's case of this kind, a girl aged eight years, each kidney was

enlarged to a longitudinal diameter of 17 cm. The interstitial tissue was replaced throughout by cellular tissue composed of closely placed small round cells, which were more numerous in the cortex than in the medulla. The tumor tissue had obliterated most of the renal structures. Metastases were present in the retro-peritoneal, tracheal and supraclavicular lymph-nodes. These authors consider the condition a primary bilateral small round-cell sarcoma of the kidney and exclude lymphosarcoma, pseudoleukemia and aleukemic leukemia. Borrmann has seen a similar diffuse sarcomatous involvement of both kidneys in an adult, without any detectable tumor elsewhere. There is some disagreement among these writers in the interpretation of their cases. Fürstenberg and Büchmann, Wehland, Borrmann, and Schwers and Wagner consider the renal involvement primary in their cases and look upon the condition as a diffuse transformation of the stroma of the kidney into sarcomatous tissue. With this view Alberran and Imbert in general agree, but suggest that the tumor tissue arises in interstitial tissue which has remained in a fetal and undifferentiated condition. v. Werdt, on the other hand, believes that in his own case and perhaps in the others the invasion of the kidneys is due to metastasis. The condition bears some similarity to the myeloid substitution in the pelvis of the kidney, which Parkes Weber has described as occurring in acute leukemia and leukosarcomatosis and to the lymphocytoblastomatosis of the kidneys of the same author.

Carcinoma, which is one of the rarer forms of tumor of the adult kidney, is quite infrequent in children. Probably all of the reported cases are mixed tumors. Monti's interesting discussion of "Nierenkrebs" in Gerhardt's Handbuch relates wholly to the mixed tumor. Phelip and Salin have reported what they consider a carcinoma of the kidney in a girl of 21 months. The tumor grew rapidly, formed a palpable mass in the left hypochondrium, and caused no urinary changes. It was composed of atypical tubules lying in fibrous stroma. The authors term the tumor an epithelioma of fetal type, but there is strong probability that this tumor also belongs to the group of mixed tumors.

Congenital Mixed Tumor.—The most important and most interesting tumor of the kidney in children is the congenital mixed tumor, several times mentioned above. The various names, sarcoma, carcinoma, sarcocarcinoma, rhabdomyosarcoma, adenosarcoma, teratoid or embryomatous tumor, which have been applied to this neoplasm, give an indication not only of its variable structure but also of the different opinions which have been held as to its nature.

Frequency.—The tumor occurs most frequently in the first five years of life. In Monti's older tabulation of 50 cases, 44 occurred during this period and six at the ages of six to nine years. The age distribution given by him for the 50 cases is as follows: During the first year, 14 cases; second year, 12; third year, eight; fourth year, eight; fifth year, two; sixth year, one; seventh year, two; eighth year, two;

ninth year, one. Walker gives the proportion of the first five years to the later years as 84 to 16 per cent. In this series 2.17 per cent. occurred in fetuses before the end of pregnancy had been reached and in 6.52 per cent. the tumor was present at birth. Dienst has reported a case in a female fetus 30 cm. long. Cases during the second decade and later are rare. Wollstein found reports of seven cases in adults from 18 to 54 years of age in a total of 97 such tumors. The condition is most often unilateral, but may be bilateral; in a total of 141 cases, 58 were of the right kidney, 73 of the left, and 10 bilateral (Walker). The two sexes are about equally affected. The proportion of mixed tumors to other tumors of the kidney in a single series of 40 renal tumors in

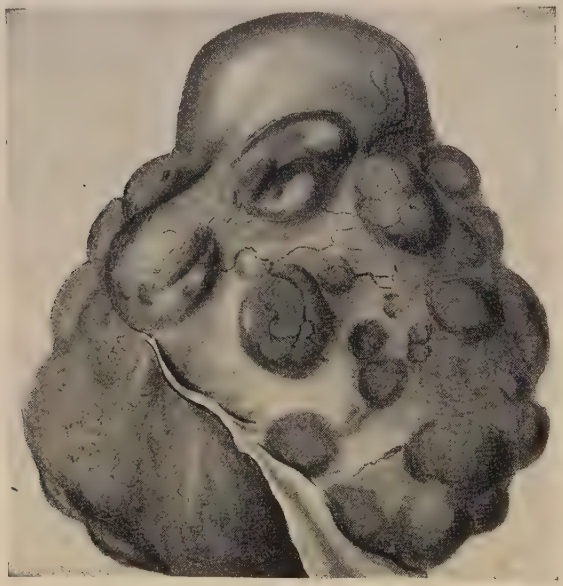

Fig. 180.—Congenital mixed tumor of the kidney. (From the collection of Dr. I. A. Abt.)

both adults and children is given by Hyman as follows: Hypernephroma, 28; mixed tumor, eight; adenocarcinoma, two; papilloma of renal pelvis, one; angioma of renal pelvis, one. Ages and sex in the eight mixed tumors were: 1½ year, male, one case; 2¾ years, female, one case; three years, female, two cases; three years, male, one case; four years, female, one case; six years, male, one case; 22 years, female, one case. The involvement in the three year old male case was bilateral.

Pathology.—The surface of the involved kidney is nodular (Fig. 180). The size varies greatly; the maximum weight found reported by Walker was 36.5 lb., the average in the reported cases where the weight was given being 6.1 lb. The tumor may already have reached such a size at the time of birth that delivery is interfered with. On section the

nodular character, apparent on the external surface, may also be quite evident. The tissue is usually rather soft, pale, semitranslucent; there may be areas of hemorrhage or of necrosis. Often a remnant of kidney tissue is present at one or the other pole of the kidney and may be rather sharply defined from the tumor tissue, indicating that the latter does not have very great invasive powers. Metastasis occurs late, according to Walker not until the vessels of the pelvis are invaded, when spread occurs by the blood stream. In Walker's series metastasis was present in half the cases.

The microscopic structure may be quite variable. The chief constituent of the tumor is a cellular sarcomatous ground substance, in which the cells may vary from round to spindle in shape. Striated muscle in varying amounts is frequently present. Other mesoblastic derivatives which have been found are cartilage, bone, adipose tissue, and mucoid stroma. It is the predominance of the sarcomatous tissue which leads to the recording of so many of these tumors as round- or spindle-cell sarcomas. Epithelial structures may be present in varying numbers. These may occur in the form of solid cellular alveoli composed of polyhedral or somewhat elongated cells; or there may be branching tubular structures which give rise to gland-like alveoli. Squamous epithelium with keratinization has been described by Ribbert and by Muus. The metastases may show the same mixed character as the original tumor. Romano described seminal tubules and adrenal tissue in a mixed tumor of the kidney.

Pathogenesis.—Concerning the origin of this kind of tumor there has been much discussion and no general agreement has yet reached. That the tumor is congenital or embryonal is established by its early occurrence and by the fact that it may even be present in the fetal period. But opinion differs as to how far back into embryologic development the origin of the condition must be thrown. Such more exact knowledge as we have of renal neoplasms is of comparatively recent development. A beginning at systematization was given when Grawitz in 1884 separated out and characterized the group of tumors to which the term hypernephroma is now generally applied. Ribbert in 1886 described a sarcoma with striated muscle elements in the kidney of a four year old girl; for this tumor and for other previously reported renal tumors with striated muscle he supposed an origin from the renal pelvis or the upper part of the ureter, the striped muscle being derived from smooth muscle by metaplasia. Six years later, as the result of the study of striped muscle containing tumors of the kidney, testicle and other regions he decided that the striated muscle in such tumors must come from misplaced muscle elements and that it is not derived from smooth muscle metaplasia. Birch-Hirschfeld (1898) emphasized the mixed character of the congenital renal tumor and attempted an explanation upon embryogenetic grounds. He derived the tumor from the inclusion within the permanent kidney of tissue derived from the primitive kidney or Wolffian body anlage. The

included tissue comes from the mesoderm at that early stage of embryonic development when this tissue has the potentiality of giving rise to the various epithelial and mesoblastic elements of the genito-urinary tract. Muus, in the following year, came to the conclusion that the mixed tumor of the kidney is derived from embryonic tissue of the kidney itself, and not from primitive kidney or Wolffian body. He held that the renal anlage itself can give rise to the various tissue elements which may occur in the tumor. Busse, in the same year, also derived the tumor from the tissue of the embryonic kidney itself, believing that this could give rise to the epithelial and mesoblastic tissues which occur and that the striated muscle arises by metaplasia from smooth muscle. In a later paper (1904) he returns to the question of metaplasia of smooth to striped muscle, the possibility of which was denied by many. He maintains his position more firmly than ever; his study of the fetal human kidney had shown that during the early fetal period smooth muscle constitutes a relatively large part of the kidney.

The necessity of explaining the presence of smooth muscle by metaplasia, the variety of tissues which may be present, and the occurrence of stratified and keratinized epithelium as noted by Ribbert and Muus, and of glial elements as described by Ribbert, constituted for many observers insurmountable obstacles to the acceptance of the views of Muus and of Busse that the mixed renal tumor is derived from the fetal kidney tissue. It was even denied that the Wolffian body anlage could give rise to all the elements which might be present, as maintained by Birch-Hirschfeld. As a result, other theories threw the origin of the tumor even farther back into the developmental period than had Birch-Hirschfeld. Wilms (1899) concluded that the tumor must arise from misplaced tissue derived from that portion of the early mesoderm which by later differentiation gives rise to the myotome (anlage of the voluntary musculature), the sclerotome (anlage of the skeletal system), and the nephrotome (anlage of the genito-urinary system). Mesodermal tissue at this stage of development would be almost, but not quite, totipotent and could theoretically give rise to a wide variety of epithelial and supporting tissues. We say "not quite" totipotent, because the presence of ectodermal derivatives, like stratified epithelium and central nervous system elements, prevented the acceptance of Wilms' theory by those who held that such derivatives must come from the ectoderm, unless one is willing to derive the middle germ layer itself from the ectoderm and to ascribe to the former the potentiality of forming all kinds of tissues. Ribbert could not admit this possibility and, therefore, derived the mixed tumors of the kidney and urogenital tract from misplaced blastomeres, cells which have the totipotent qualities of the fertilized ovum from which the blastomeres are derived in the early segmentation stage.

To recapitulate, then, the theories of origin of the congenital mixed tumors of the kidney, we have the following: (1) The tumor is derived

from the tissue of the fetal kidney itself, after the kidney has been differentiated off from the rest of the primitive urogenital system (Busse, Muus). The process which leads to the failure of normal differentiation of an area of fetal renal tissue is a developmental anomaly of the "Hemmungsbildung" type, the later development of a tumor being the result of the initiation of growth processes in the undifferentiated tissue. It is necessary to include the possibility of metaplasia to explain the derivation of certain of the tumor elements, like striped muscle, squamous epithelium, etc. (2) The tumor takes its origin at a somewhat earlier period of embryogenesis from the anlage of the primitive kidney or Wolffian body, at a stage when the latter has not yet given rise to definite renal tissue (Birch-Hirschfeld). (3) The tumor arises at a still earlier period, before the mesoderm of the mid-dorsal region has given rise to myotome, sclerotome or nephrotome (Wilms). (4) The tumor is developed from a totipotent blastomere, misplaced at a stage of development before the three primitive germ layers have been formed (Ribbert). The three last named theories presuppose the inclusion of the misplaced tissue in the anlage of the fetal kidney. In all of the theories there is no explanation of the process or force which initiates the unlimited proliferation of the undifferentiated or misplaced tissue. This, of course, is the fundamental and still unsolved riddle of all malignant tumors. One of the unanswered questions for the future is why the tissue which gives rise to a mixed renal tumor does so during the fetal period or during the first years of life, whereas the hypernephroma, which is also derived from fetal tissue, adrenal if one agrees with Grawitz or nephrogenic if one accepts Wilson's views, does not develop until the early or middle period of adult life.

FIG. 181.—Abdominal enlargement in congenital mixed tumor of the kidney. (From the collection of Dr. I. A. Abt.)

Symptoms.—Clinically the congenital mixed tumor of the kidney is characterized by the large size which the tumor may reach, by the absence of pain, and by the apparent good health of the child until the terminal stage is reached. The urine usually shows no changes; by cystoscopy and ureteral catheterization, decreased or absent urine output from the involved kidney may be detected. Hematuria may

occur but is infrequent; when blood is present it is usually in microscopic quantities. The relative infrequenc of hematuria is in striking contrast with the findings in hypernephroma. In most cases a palpable tumor mass or visible enlargement of the abdomen is the first evidence of the tumor (Fig. 181). If the latter grows rapidly pain may be present. In 120 of the cases collected by Walker, tumor was the first symptom in 38, pain in 14, hematuria in 14, and weakness in 10. In the final stage, emaciation and cachexia become marked.

Treatment.—Although the neoplasm, during a great part of the earlier stages of its course, has no very marked tendency to invade the kidney tissue or surrounding structures, it leads inevitably to death and the operative results are very discouraging. Because of the symptomless course of the condition, the diagnosis is not made until the tumor has broken away from the kidney; for this reason nephrectomy is followed by recurrence and death in a very large percentage of cases. Surgical removal of the involved kidney is the only treatment which offers any hope whatever; better results can come only from earlier diagnosis. How unsatisfactory the results are is apparent from the statistics given by Walker. The immediate mortality in his tabulation was 38.25 per cent.; the ultimate mortality was 74.32 to 94.53 per cent.; cure was obtained in only 5.47 per cent. The average duration of life without operation was 8.08 months; with operation it was 16.77 months. Roentgen-ray therapy apparently offers no hope; in an inoperable case thus treated by Friedlander radiation was without effect.

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CHAPTER CII

POSTURAL ALBUMINURIA

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An appreciable amount of albumin in urine voided while in the upright position and its disappearance when the recumbent position is assumed is referred to as postural albuminuria.

In 1878, Moxon,[1] who was one of the earliest writers to draw attention to the occurrence of an albuminuria unassociated with other evidences of renal disease, described two types of cases, those with "adolescent albuminuria" and those with "remittent albuminuria." In the latter, the albumin appeared after the patient had been up and about for some time, whereas the urine voided immediately on rising was albumin-free. Soon after this observation, a number of similar cases were reported and in 1885, Pavy[2] demonstrated the intermittent appearance of albumin in the urine of children and young adults. He called this *cyclical albuminuria* because of its disappearance in the morning urine and its reappearance in the urine voided throughout the day. Pavy and the observers preceding him did not recognize the importance of posture in this form of albuminuria. They thought that it was dependent on fatigue, cold, exercise and many different physiologic conditions. The importance of posture was not emphasized until 1887 when Stirling[3] showed that the albuminuria disappeared completely in the prolonged recumbent position and that it reappeared immediately in the upright position. Heubner,[4] because of the influence of the upright posture, suggested the term *orthotic albuminuria*. Jehle,[5] who believes that the albuminuria is invariably associated with a lordosis, speaks of it as *lordotic albuminuria*. *Postural albuminuria* is the term of preference, as the albuminuria is dependent on the change in posture.

This is a well-recognized condition and one met with not infrequently. Probably the majority of cases are seen in children's clinics where routine examinations of urine are made. In one series of cases that has been reported, postural albuminuria was found in 39 per cent. of 223 children. This form of albuminuria should always be kept in mind when albumin can be demonstrated in the urine of children.

Postural albuminuria is rarely seen in infancy or early childhood. It is found with increasing frequency until the age of puberty, after which the incidence diminishes quite rapidly and becomes infrequent during adult life. A few cases have been reported as early as the

third year of life but the largest number are seen between the sixth and the sixteenth years. In one series, 69 per cent. of the cases occurred between the eleventh and the fourteenth years. It is equally common among both sexes and more than one child in the same family may be affected.

Many of the children with postural albuminuria present such a characteristic clinical picture that they suggest at once the possibility of this condition to the experienced observer. They are tall, slender, poorly nourished and have what is commonly referred to as a "sway back" (lumbar lordosis). In addition, they appear anemic. This anemia, however, is more apparent than real, as the hemoglobin index is normal. They suffer from emotional disturbances, headache, gastro-intestinal symptoms, palpitation of the heart and various functional disturbances. These children often exhibit a neuropathic tendency. These symptoms are not due to nor are they the result of the albuminuria. On the other hand, the albuminuria may be found in strong, vigorous and apparently normal children. In them it is often discovered by accident during the course of a routine examination of the urine or when they are ill with an unassociated disease.

No subjective symptoms characteristic of the condition occur. The attempt has been made to correlate the rapid pulse, the arrhythmia and the accidental heart murmurs, which are frequently present in these patients, with the albuminuria, but as yet there is no well-established basis for such an association. The blood pressure is normal and a hypertension has not been recorded in patients with postural albuminuria. Edema does not occur. The only objective symptom is a lumbar lordosis and for that reason postural albuminuria should be considered in patients with this deformity. It must be remembered, however, that many individuals with lumbar lordosis do not have an albuminuria even when an exaggeration of the lordotic posture is induced.

The following history of a patient, whom I have had under observation for several years, illustrates very well the important features of postural albuminuria. During the course of an attack of angioneurotic edema, when he was eight years old, albumin was found in the urine. The physician observed that though the edema about the eyes became less, the albuminuria persisted. It was constantly present in the specimens of urine examined but it varied in amount from time to time. The albumin became less with rest in bed, a milk diet and diuretics but as it did not disappear entirely, he was admitted to the hospital. He was a tall, slender, fairly well-nourished boy, who appeared very anemic. When he stood erect, the appearance of his back was characteristic. There was an extreme lordosis, most marked in the upper lumbar region. Examination of the urine which was voided when he was in the upright position showed albumin. It was present in such a large amount that with the heat and acetic acid test, the urine solidified. A specimen of urine obtained after he

had been in the recumbent position for some time did not contain albumin. There were no formed elements. The blood pressure was normal and an anemia was not present. When seen at the age of 14 years, the albuminuria had disappeared. It is interesting, however, that the lordosis continued to be as marked as when he was first examined.

The important causative factor in this condition is the posture. The albuminuria disappears completely in the recumbent position and reappears immediately as soon as the upright position is assumed. The appearance and disappearance of the albumin can be influenced at will as the only factor for its production is the change from the horizontal to the vertical position. This is the reason for the appearance of the albuminuria during the day and its disappearance during the night.

Two albuminous substances are present in the urine of these patients: The one, true serum albumin, and the other, a substance precipitated by acetic acid without the assistance of heat. The nature of this latter body is disputed. It has been believed by some to be a nucleo-albumin, by others to be euglobin and more recently, it has been asserted by Pollitzer[6] to be chondroitin-sulphuric acid. Pollitzer and others lay great stress on the presence of this substance in the urine and believe that it indicates pathologic changes in the kidneys. Jehle[5] considers the presence of this substance significant of postural albuminuria. While it may be found both in the urine of children with postural albuminuria and in those with nephritis, it is also found, in small amount, in the urine of normal children. Its presence alone does not indicate postural albuminuria but there is no other condition in which it is found in such amount without a very much greater quantity of serum albumin.

The amount of albumin in the urine varies greatly. In the upright posture, there may be either a slight or a marked trace but when the extreme lordotic posture is assumed, the quantity of albumin may be increased so that the urine becomes almost solid upon boiling. In one of my patients with a high degree of lordosis, 10 gm. of albumin per liter were excreted but ordinarily the quantity does not exceed 2 or 3 gm. per liter.

The very wide differences of opinion concerning the presence or absence of formed elements has led to much confusion. Heubner,[4] Langstein[7] and others take the position that the presence of casts and leukocytes is sufficient evidence of a nephritis and that the case is not one of postural albuminuria when they are found. Goetzky[8] favors the view of Heubner, but makes the differentiation still more confusing by adding a separate group of nephritic patients in whom the albuminuria is dependent on posture. Jehle[5] and others believe that formed elements may be present in postural albuminuria without being significant of nephritis. He is influenced by Senator[9] who found casts in the urine after congestion of the kidneys and also by the fact that they

may be found after exercise. Jehle's[5] recent work is of special interest; he has shown that the portions of urine obtained after the lordotic posture has been maintained for 10 to 15 minutes may contain hyaline or granular casts and leukocytes. In 14 cases observed by the writer, casts were found in only one. This patient, eight and a half years old, was admitted to the hospital because of enuresis. He was a well-nourished and well-developed boy whose physical examination was negative except for a well-marked upper lumbar lordosis. There was no albumin in the urine when he was in the recumbent posture. After the upright posture there was a trace of albumin and after being in the forced lordotic posture for 10 minutes, there was a heavy precipitate. Many hyaline and hyalo-granular casts and leukocytes were present in the urine after the lordotic posture. It is now generally believed that casts and leukocytes may be present in the urine in this condition and that they are not indicative of a structural change in the kidneys.

Many studies have been undertaken to determine the efficiency of the kidneys. Nobecourt,[10] Courcoux[11] and others found the renal function test normal. Linossier and Lemoine[12] and Jehle[5] demonstrated an oliguria with retention of sodium chlorid. The latter showed that the oliguria and the retention of sodium chlorid varied with the degree of albuminuria. When the lordotic posture was maintained for a long time, and when there was a marked albuminuria, there was an oliguria and a marked retention of sodium chlorid. This was less marked with a mild albuminuria and disappeared entirely in the recumbent posture when there was no albuminuria. Jehle was able to demonstrate the same conditions in the urine of normal children in whom an albuminuria was caused by compression of the abdominal aorta. Hempleman[13] found that the efficiency of the kidneys as measured by the phenolsulphonephthalein test was normal when the patients were at rest in bed but when they were placed in a position of extreme lordosis, which produced a marked albuminuria, the total output of phenolsulphonephthalein in two hours was reduced. The consensus of opinion is that the oliguria, the retention of sodium chlorid and the diminution of phenolsulphonephthalein, which are only found when the patient is in the position producing a marked albuminuria, are the result of a mechanical interference with renal circulation and that there is no reason to think that the albuminuria is due to an organic renal lesion.

But little information regarding this condition has been obtained from histologic studies of the kidneys as fatal terminations are uncommon. In Heubner's[4] patient, the only case reported in the literature, death occurred as the result of a cerebellar tumor, two years after the albuminuria was discovered. Careful histologic examination of the kidneys failed to reveal inflammatory or degenerative changes sufficient to account for the albuminuria.

The manner in which the albuminuria is produced is not clearly understood. In all probability it is brought about as the result of a

congestion of the kidneys. This may be caused, in the pre-disposed patient during the upright position, by direct pressure on the renal veins or by indirect pressure on the inferior vena cava by a change in the position of the diaphragm. Vasomotor disturbances, a peculiar permeability of the kidneys and the various other causes which have been suggested are factors which play a relatively unimportant part. Jehle[5] has advanced the theory that the albuminuria is caused by a lordosis in the upper lumbar region. By the use of an apparatus which reproduced the exact contour of the spinal column. He demonstrated an "upper lumbar lordosis" in his patients with this form of albuminuria. The effect of an induced lordosis with the patient in the recumbent position is variable and the albuminuria cannot be produced with regularity. Whilst the influence of lordosis is well recognized, it should not be considered the only factor necessary for the production of the albuminuria. Pollitzer has maintained that patients with postural albuminuria have a subnormal type of constitutional development and that the maintenance of the upright posture with perfect physiologic function, therefore, is prevented. He refers to this as a "static neurosis" and believes that the albuminuria is not caused entirely by the upright posture, but occurs because the kidneys are more susceptible to the development of slight lesions with mild infections. The strongest argument against Pollitzer's idea is the regularity with which the albuminuria disappears with increasing age. This scarcely would be expected if the albuminuria was due to a pathologic renal lesion as in children the tendency is for such lesions to become more extensive rather than less so. Although the exact cause of the albuminuria cannot be definitely stated, the following factors are necessary for its production: (1) The erect posture; (2) the maintenance of this posture with rigid contraction of the back muscles; and (3) a certain pre-disposition on the part of the patient. This pre-disposition is dependent on a purely anatomical basis. A lordosis may or may not be associated but when it is present the albuminuria is apt to be more marked.

The diagnosis is established by demonstrating an albuminuria when the patient assumes the upright posture and its disappearance in the recumbent posture. It may become much more marked with the patient in an exaggerated lordotic posture. This posture is induced by having the patient stand with the head and the heels against the wall and with the back arched. After maintaining this position from 10 to 20 minutes, the specimen of urine voided usually contains a marked increase in the amount of albumin as compared with the amount in the upright position. The albuminuria tends to persist for a short time after the upright posture, so a few minutes should elapse before obtaining a specimen of urine from the patient in the recumbent posture. The bladder also should be *completely* emptied, before the specimen is obtained between the upright and the recumbent positions. The presence of casts and leukocytes does not exclude the

diagnosis of postural albuminuria. When for any reason there is a question as to the diagnosis, the patient should be kept under observation and the postural tests repeated. The diagnosis between postural albuminuria and a nephritis depends chiefly upon the relation between the postural tests and the albuminuria, and the absence of other evidences of nephritis (hypertension, hypertrophy of the left ventricle of the heart and the renal function tests). In patients convalescent from a nephritis, albumin may appear in the urine when they first are allowed out of bed. Janeway emphasizing the importance of this wrote: "Where there has been an acute nephritis, and you are watching merely the disappearance of albumin, the patient should be kept at rest as long as possible, even if the albumin only reappears on standing. In patients with postural albuminuria who have not had an acute nephritis, exercise helps to make a differentiation. Exercise will frequently fail to produce an albuminuria in these patients. So far as my experience goes, a true nephritic albuminuria which is brought out by standing will be brought out even more markedly by active physical exercise." When an excessive precipitate with acetic acid in the unheated urine is found, postural albuminuria should always be considered. Large amounts of this precipitate are found in amyloid disease but the differentiation between these two conditions is easily established by the disappearance of the albuminuria in the recumbent posture.

The prognosis in postural albuminuria is excellent. A few cases are reported in which the albuminuria has persisted throughout adult life, but in the majority of patients it disappears during adolescence. There is no record of a patient with a postural albuminuria having subsequently developed a nephritis. The course is distinctly a chronic one and as remissions of weeks or months in the appearance of the albuminuria occur, it is often difficult to determine when the process has subsided.

The treatment should be directed toward the improvement of the general physical condition of the patient. Mechanical and gymnastic measures are recommended to strengthen the muscles of the back and to correct the lordosis when it is present. Rest in bed is not advisable and the enforcement of a strictly milk diet and other therapeutic measures to influence the harmless albuminuria are contra-indicated.

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CHAPTER CIII

THE URINE IN INFANCY AND CHILDHOOD

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As the blood passes through the kidney, it loses some of its constituents. These are removed from the body in watery solution. Leaving the morphologic elements of the blood out of consideration, there are obviously marked differences between blood plasma and urine. Aside from the more or less complete absence of proteins from the urine, the concentration of certain substances, notably creatinin* and urea, is much greater in the urine. The mechanism by which this is brought about is by no means fully known. A popular explanation is that the blood pressure in the glomeruli, exceeding the osmotic pressure of the proteins, forces fluid through the walls of the capillaries. This fluid contains the soluble constituents of the blood other than proteins. As the fluid passes through the tubules, the greater part of it, together with some of the substances dissolved in it, is reabsorbed.† This conception denies that the tubules have any secretory function. Filtration through the glomeruli has been accepted by many as part of the secretory mechanism, together with absorption by the tubules. A secretory function has also been reserved for the tubules.[237] With regard to filtration, it has not been emphasized sufficiently that, besides the capillary walls, the capsule of Bowman has to be considered. Moreover, filtration of a complex fluid may not be as simple a process as the filtration of water through filterpaper. In sharp contrast to this theory is the statement of Volhard: "The question is no longer whether filtration and re-absorption play a rôle in the production of urine by the normal kidney, but why it is that neither filtration, nor re-absorption, nor diffusion, nor osmosis take their part in the normal kidney to equalize the differences of concentration between blood and urine. What enables the epithelial cells of the kidney to master these physical forces to which they succumb under pathologic conditions?—The chemical and physical processes which take place when the kidney does its secretory work are not known." Volhard summarized the mechanism or urinary secretion in that glomeruli

* Behre and Benedict claim that the concentration of creatinin, if this substance occurs at all in blood, cannot be more than 0.05 mg. for each 100 c.c. of blood, and that the kidney normally eliminates creatin as creatinin. But even so, the concentration of creatinin in the urine far exceeds that of creatin and creatinin in blood.

† This view, based chiefly on the work of Starling, has been emphasized particularly by Cushny.

and tubules secrete the same dissolved substances, but in different concentration. The special function of the glomeruli is dilution. The special function of the tubules is concentration

Laws of urinary secretion have been advanced by Ambard. Taking as example urea he states the following laws:

1. When the kidney eliminates urea at a constant concentration, its amount varies in proportion to the square of the concentration of urea in the blood. For instance with an increase of a urea concentration in the blood of from 0.25 to 0.5 for each 1000, the amount of area in the urine being at the initial blood concentration 10 gm., becomes 40 gm. Or if the concentration of the urea in the blood increases as 1:2:3, the amount of urea excreted by the kidney increases $1:2^2:3^2$ times the initial amount in the urine.

2. When with a constant concentration of urea in the blood, the subject eliminates urea at variable concentrations, the amount of urea excreted is inversely proportional to the square root of the urea concentration in the urine. For convenience of comparison, the results can be reduced to a standard of 25 for each 1000 urea in urine, so that $\frac{D25}{D} = \frac{\sqrt{C}}{\sqrt{25}}$ or $D25 = \frac{D \times \sqrt{C}}{5}$.

3. When all three factors, urea concentration in the blood and in the urine, as well as the amount of urea excreted, vary, it follows that the amount of urea varies in direct proportion to the square of the urea concentration in the blood, and in inverse proportion to the square root of the concentration of urea in the urine. This leads to the ureosecretory constant $K = \frac{Ur}{\sqrt{\frac{D \times \sqrt{C}}{5}}}$. A correction for weight may be made, since this constant is dependent on the parenchyma of the kidney, and the weight of the kidney is approximately proportional to the bodyweight. The correction is made, taking as a conventional standard weight 70 kg. For instance with a subject of 35 kg., $D25$ was found to be 15; the correction would then be $\frac{15 \times 70}{35} = 30$. This with a urea concentration of 0.3 in the blood give $K = \frac{0.3}{\sqrt{30}}$. It is to be noted that the concentration of urea in the blood is determined and expressed for each liter. This is the Ur of the formula. The blood is obtained at a time exactly half-way between the beginning and end of the urine collection, which extends only over a period of one to two hours. The volume of urine actually collected in the given short period of time is multiplied so as to represent a 24 hour volume. The amount of urea is determined in the specimen of urine collected, and the amount of urea in grams for the calculated volume of urine for 24 hours. This amount of urea in grams is the D of the formula; it is the amount which would have been excreted in 24 hours provided a uniform rate of excretion had obtained. The C of the formula designates the concentration of urea for each liter

in the specimen collected. The constant for urea has been found to be approximately 0.07 in adults as well as in children. The secretory constant holds good for other substances. The formula is applicable for no threshold substances like urea, which are excreted as long as there is any left in the blood. In the case of threshold substances such as sodium chlorid, where the concentration of the substance in the blood must reach a certain level before excretion through the kidney takes place, this threshold value has to be taken in consideration. Changes in the Ambard constant and coefficient are supposed to indicate changes in renal function. The laws of Ambard, it must be stated, have not as yet been accepted universally. McLean accepted as the normal value for K, 0.08, and proposed in place of the Ambard constant an index of urea excretion I, an index of 100 corresponding to Ambard's $K = 0.08$. An index of 50 means a rate of excretion 50 per cent. of normal under the conditions of concentration in blood and urine. The formula is

$$\text{Index} = \frac{\text{gram urea per 24 hours}\sqrt{\text{gram urea per liter of urine}} \times 8.96}{\text{weight in kilos.} \times (\text{gram urea per liter of blood})^2}$$

Composition of the Urine.—The composition of the urine is chiefly dependent on the processes of metabolism. The composition of the urine cannot be studied separately from metabolism, except in a fragmentary manner. The metabolism of the child does not differ in its fundamental aspects from that of the adults. Therefore substances intimately connected with the metabolic exchanges which are found in the urine of the adult are to be found in the urine of the infant and child. If some such substances have not been demonstrated as yet, this may be due to the greater difficulty of collecting urine in sufficient quantities from infants and children in a manner free from objection. While in the main the metabolism of the child is like that of the adult, there are certain factors which must exercise an influence on the metabolism and consequently on the composition of the urine. Growth is one of these, even though we cannot determine the manner in which this factor is represented in the composition of the urine. Another factor is the maturing of the sex glands, and still another lies in the changed proportion which the different organic systems assume in the body of the adults. For instance the body of the child has relatively less muscle and more skin than that of the adult. Such differences should be reflected in the metabolism, and consequently in the composition of the urine.

Amount of Urine Excreted.—The amount of urine voided daily is dependent primarily on the amount of fluid ingested. In older children the water contained in solid food may be not inconsiderable. The water derived from oxidation of food such as carbohydrates has to be considered in very exact work. The amount is furthermore dependent on the amount of water given off in the feces, and by lungs and skin. During about the first year of life it is unusual for an infant to produce sweat on any other place than the head. Nevertheless it

seems that the loss of water vapor through the skin may become considerable under certain conditions.[225]

The table in Holt's textbook of pediatrics (Table 1), indicating the amount of urine excreted at different periods of infancy and childhood may be useful, if it is kept in mind that, aside from variations of individuals, the variations in the same individual from day to day may be very marked. For the ages from two years on, the lower limits indicated are perhaps a little too high. Not infrequently newborn infants do not void on the first day, and they may go even longer without voiding.

TABLE 1.—AVERAGE DAILY QUANTITY OF URINE IN HEALTH (HOLT)

Age	Grams
First 24 hours	0–60
Second 24 hours	10–90
Three to six days	90–250
Seven days to two months	150–400
Two to six months	210–500
Six months to two years	250–600
Two to five years	500–800
Five to eight years	600–1200
Eight to fourteen years	1000–1500

Interesting data have been published by Engel[92] who placed infants during the first year of life on a metabolism frame, and collected the urine in a flask armed with electrodes arranged so that the passage of the urine closed an electric current giving a signal with a bell. On an average a normal infant voided about 25 times in 24 hours on a food intake of 750 c.c. With an increase in the amount of fluid intake, the frequency rose to as high as 70. According to Pfeifer an increase of the frequency of urination may occur without increasing the fluid intake. In the majority of Engel's observations, 10 to 20 c.c. of urine was voided at one time. Depending on the interval between voidings, a single discharge may rise to 50 or 60 c.c., and exceptionally to 70 or 90 c.c. During sleep practically no urine was passed. On an intake of 400 to 900 c.c. Pfeifer observed an average of 18 urinations in infants whom he says were distinctly not normal. In these cases there was not much difference between the baby asleep and the baby awake. A seven weeks old breast fed girl with an ectopia vesicæ offered Tugendreich a singular opportunity for studying the urine secretion. In conformity with an observation of Suter and Meyer on a boy five years of age with the same abnormality, the right ureter discharged more urine than the left. During sleep the secretion of urine was markedly diminished.

Camerer found that an infant excretes 68 to 70 per cent. of the ingested fluid in the urine. In some cases reported in the literature

this percentage was not reached. Nevertheless it is generally accepted that the normal infant during the first year of life on a proper diet and under proper conditions excretes about two-thirds of the fluid intake in the urine.

The first days of life are exceptional. The fluid intake is rather inconsiderable and relatively less of the introduced fluid appears in the urine. This latter condition is more noticeable in the breast fed infant with its smaller quantity of milk. The table of Reusing records the findings in a series of newborn infants, the breast fed and the artificially fed being listed separately.

Table 2.—Findings in Newborn Infants with Regard to Fluid Intake and Excretion (Reusing)

Day	Quantity of milk, cubic centimeters		Quantity of urine, cubic centimeters		Urine in per cent. of milk	
	Bottle fed	Breast fed	Bottle fed	Breast fed	Bottle fed	Breast fed
1	96	38	36	8	37	22
2	150	121	71	27	47	22
3	229	177	136	41	59	23
4	253	220	187	61	74	28
5	365	272	283	119	78	44
6	369	296	246	149	67	50
7	410	297	325	157	79	58
8	530	338	406	208	77	63

Table 2 shows that the urine increases regularly from day to day. In individual cases, however, wide daily variations may occur.

A definite influence of additions to the diet has been observed. Niemann[277] added to the diet of infants 40 to 50 gm. of carbohydrate, and observed in some of them a very decided diminution of the urinary secretion. Such results were obtained with lactose, rye flour, Soxhlet "Nährzucker," but not with cane sugar. The results were obtained in infants doing well on a diet relatively rich in carbohydrate. The number of observations, however, is not very great Addition of fat to the diet may also be followed by a diminution of the urinary secretion (Mayerhofer). Under certain conditions it is well known that addition of table salt leads to a retention of water, and a retention of water occurs in fevers.[218] Under such conditions the urine becomes scanty.

In diabetes mellitus and particularly in diabetes insipidus the urine excretion increases markedly.

The effect of various factors on the amount of urinary secretion has been studied recently by Aschenheim[27] employing the "water

test" of Strauss-Volhard. The infants received their last food at 9 p.m. At 6 a.m. they received 200 c.c. distilled water, or water to which sodium chlorid or sugar had been added. The urine was collected from 6 to 11 a.m. With sodium chlorid (physiologic salt solution) lactose and Soxhlet "Nährzucker," less water was excreted than when water alone was given. Cane sugar did not have this effect. When an infant had been kept on concentrated food for a period of time, more water was retained. Attention will be called but briefly to another method of study employed by Aschenheim. The urine excretion on withholding food and fluid for several hours has been designated by Pollitzer, "specific diuresis." During the first three months of life, Aschenheim found this specific diuresis rather small. Ohlmann applied the "water test" to a larger number of infants and older children, using water and 0.7 per cent. sodium chloride solution. Infants under nine months of age taken as a group excreted decidedly less water and much less of the saline than the older children.

In these investigations the extrarenal loss of water was not taken in consideration, and Stransky and Weber could not confirm these findings. Neither did Wengraf, who found that even in the youngest breast fed infant in good health the water excretion exceeded the intake under the conditions of the experiment. This, Mendel found to be the case also in children. The results of Lasch, who took the specific diuresis also in consideration, showed that during the first month of life the total water excretion is on the whole less than later on. His figures, taking into consideration only well developing infants of normal weight, may be cited; in the first month 106 per cent. of the intake was excreted (six cases), in the second and third 150 per cent. (seven cases). This inhibition shows particularly in the urine excretion, while the insensible perspiration tries to equalize the water excretion. Stransky and Kochmann distinguish between two types of water excretion in the infant, according to the preponderance of the renal or extrarenal route.

Properties of Urine Not Discussed.—Certain properties of urine, including the lowering of the freezing point, viscosity, surface tension, electrical conductivity, the presence of some colloidal (non-dialysable) substances other than protein, and of gases, cannot be treated here, partly because the data at our disposal are insufficient, partly because their significance is too obscure.

Color, Odor, Specific Gravity, and Reaction of Urine.—The urine is a deeper yellow during the first few days of life than later. During infancy it varies from nearly colorless to light yellow, and deepens gradually with advancing age to that of the adult urine. The color of normal urine has been attributed to a pigment called "urochrome" whose chemical constitution has not been determined. But, according to Weiss[400], there is no single substance in urine deserving this name. Several different dyes and chromogens make up the color of the urine. These are derived from endogenous and probably

also from exogenous sources. The urine contains normally urochromogen, which on oxidation gives a yellow color. To this Weiss[401] attributed the diazo-reaction of Ehrlich. It contains nitrogen and sulphur, and is derived from tissue catabolism. Its excretion for each kilogram of body-weight is somewhat greater in the child than in the adult, who excretes on an average about 0.06 gm. a day. Table 3 gives in convenient form the main changes of color which occur in urine. The table is given in its original form although some of the pathologic conditions stated are very uncommon in childhood. To these may be added the development of a dark-brown to blackish color on addition of sodium hydroxid to urine containing homogentisic acid (alkaptonuria). An abundant supply of carrots in the diet may give the urine an intensified yellow color.

Hemoglobinuria, that is the appearance of dissolved hemoglobin in the urine, may occur in the course of various infections. One of these, Winckel's disease of the newborn, goes under the name of hemoglobinuria epidemica. Hemoglobinuria also occurs in certain intoxications. Of greater interest are the cases of paroxysmal hemoglobinuria, in which hemoglobin passes in the urine on exposure of the patient to cold. The majority of cases are referable to hereditary syphilis, and while antisyphilitic treatment may not afford a complete cure, it has often caused marked improvement. Reiss asserts that during the attack autohemolysis occurs in the body, even if it cannot be shown always in vitro. The resistance of the erythrocytes is diminished in these cases, particularly during an attack.

Under certain conditions, hematoporphyrin (iron free hematin), a derivative of hemoglobin, appears in the urine imparting to it a burgundy-red or darker color. In urines containing this substance the occurrence of a chromogen called urofuscin has been described. Günther distinguishes four forms, (1) hematoporphyrinuria acuta; he describes the case of a seven year old boy, who had suffered for two years with attacks of recurrent vomiting; (2) hematoporphyrinuria acuta toxica which occurs in intoxications with sulphonal, trional and veronal; (3) hematoporphyrinuria chronica; this may exist for long periods without particular disturbances aside from a hypersensitiveness of the skin to light, and (4) hematoporphyrinuria congenita. In eight cases collected from the literature one or another symptom pointed to its beginning in early childhood, not always very convincingly. In one case red urine was noted at the age of 20 months, and in the case reported by Günther the urine had been dark and occasionally black, ever since the patient, a young man, was two years old. In another case of congenital porphyrinuria, the milk teeth were colored a deep pink.[227] Of particular interest in these cases, in which the hematoporphyrinuria lasts for some time, is the hypersensitiveness of the skin to light. Injections of hematoporphyrin in animals may lead to severe illness or death on exposure to light.

The newborn infant's urine has very little odor or taste. Later the odor is like that of adult urine. The characteristic odor of urine has

TABLE 3.—CHANGES OF COLOR IN THE URINE (HALLIBURTON)

Color	Cause of coloration	Pathologic condition
Nearly colorless.....	Dilution, or diminution pigment	Nervous conditions: hyruria diabetes insipidus, granular kidney
Dark yellow to brown red.	Increase of normal, or occurrence of pathologic pigments. Concentrated urine	Acute febrile diseases
Milky.....	Fat globules Pus corpuscles	Chyluria Purulent diseases of the urinary tract
Orange.....	Excreted drugs	Santonin, chrysophanic acid
Red or reddish.....	Unchanged hemoglobin Pigments in food (logwood, madder, bilberries, fuchsin)	Hemorrhage or hemoglobinuria
Brown to brown-black...	Hematin Methemoglobin Melanin Hydrochinon and catechol	Small hemorrhages Methemoglobinuria Melanotic sarcoma Carbolic acid intoxication
Greenish yellow, greenish-brown, approaching black.	Bile pigments	Jaundice
Dirty green or blue.....	A dark blue scum on surface, with a blue deposit, due to an excess of indigo-forming substances	Cholera, typhoid fever seen particularly on putrefaction of the urine
Yellowish brown to red brown, on addition of alkali blood red.	Substances introduced into organism with senna, rhubarb and chelidonium	

been ascribed by Dehn and Hartman to a definite chemical compound which they isolated and called urinod. But this urinod seems to be a mixture of substances.[18] As a rule the urine of the first few days is more or less turbid, owing to the presence of epithelial cells of the urinary tract and of urates. Later on, the urine clears. The specific gravity of the urine during the first few days of life is high, sometimes

reaching 1.013. After the fourth day it drops, and in the normal breast fed infant, remains about 1.004 during the first year. Holt tabulates it thus:

First to third day	1.010–1.012
Fourth to tenth day	1.004–1.008
Tenth day to sixth month	1.004–1.010
Six months to two years	1.006–1.012
Two to eight years	1.008–1.016
Eight to fourteen years	1.012–1.020

The reaction of the urine the first days of life is as a rule markedly acid to litmus; later, in the breast fed infant, it is usually weakly acid, sometimes neutral, or even alkaline to this indicator. Its reaction to phenolphthalein is always acid. The urine of the infant fed on cow's milk mixtures is usually decidedly acid to litmus. The reaction depends on the relative amount of acid and basic substances in the urine. The secretion of such substances by the kidney constitutes one of the regulatory mechanisms by which the organism maintains the reaction of the blood and tissues at the proper level. Indicators changes their color at a definite hydrogen-ion concentration. By choosing suitable indicators and comparing the color produced in the urine with that produced in a solution of known hydrogen-ion concentration under otherwise similar conditions, the hydrogen-ion concentration can be determined with a good degree of accuracy. This principle underlies the methods generally used in clinical laboratories.*

In this connection, a few facts should be kept in mind. Saying a urine has a certain hydrogen-ion concentration means that its reaction is like that of a solution containing a given number of hydrogen-ions in one liter of water, and further that a hydrogen-ion concentration of one means 1 gm. of hydrogen-ions in one liter of water, and that this is equivalent to a normal solution of an ideal, that is a completely dissociated, acid. A normal or grammolecular solution of an acid, which does not dissociate completely, will have a smaller number of hydrogen-ions for each liter and therefore a smaller hydrogen-ion concentration, depending on its degree of dissociation, for instance, that of acetic acid being many times less than that of hydrochloric acid. Nevertheless a grammolecular solution of acetic acid (the molecular weight of the acid dissolved in a liter of water) will neutralize as much alkali as a grammolecular solution of hydrochloric. But as far as its true or actual acidity is concerned, it is a much weaker acid, and this finds its expression in its hydrogen-ion concentration.

Pure water obtained under special precautions is neutral; it contains for each liter .0000001 gm. hydrogen-ions or 1×10^{-7}. Instead of speaking of a hydroxyl-ion concentration to denote alkalinity in the same way, it was found convenient to continue the series of hydrogen-ion concentration to 1×10^{-8}, and so forth. To avoid cumbersome numbers such as 0.35×10^{-7} Sorenson introduced the hydrogen-ion exponent with its symbol P_H. For instance instead of writing 2×10^{-7} one takes log 2 = 0.3 and $1 \times 10^{-7+0.3}$ or $P_H = 6.7$. A tenth normal solution of a strong acid has a P_H = about 1, a hundredth normal solution, a P_H = about 2, and so forth; a $P_H = 7$ denotes neutrality, $P_H = >7$ therefore acidity, and the higher the degree of acidity or its intensity, the smaller the P_H. A $P_H \times < 7$ denotes alkalinity, and the greater the alkalinity the greater the P_H; P_H = about 14, means an *about* decinormal solution of a strong alkali. From a $P_H = 7$ to a P_H

* With regard to the determination of true acidity and methods, see Michaelis "Die Wasserstoffionenkomzentration" and Clark, W. M.: The determination of hydrogen ions. Baltimore, Williams and Wilkins, 1922, 480 pp.

= 6, the hydrogen-ion concentration increases 10 times. But an increase of a hydrogen-ion concentration to double its amount, say from 1×10^{-6} to 2×10^{-6}, does not give a P_H =5.5, but log 2 = 0.3 and $1 \times 10^{-6+0.3}$ of P_H = 5.7.

The hydrogen-ion concentration of the urine of the normal adult on a general diet is given by Henderson and Palmer as P_H = 5.1 to 7.0 for the 24 hour specimens, while the P_H of single specimens varied from 5.0 to 7.4. Many of the earlier determinations on infants were made on single specimens. For certain types of information, it is necessary to study single specimens; but for the determination of average values, and for comparsion of the effect of varied forms of diet, it is better to make determinations on 24 hour collections of urine. The urine of a few normal breast fed infants gave a P_H of 5.5. to 7.2.[409] Twenty-four hour specimens of a premature infant were tested at various times during six months, the P_H dropping from 5.4 to 7.2 with advancing age. The urine of a newborn infant before feeding gave a P_H = 6. Ylppö obtained P_H higher than 5.0 only under abnormal conditions. The normal breast fed infant, Case 6 of Stenström excreted for six days a 24 hour urine with a P_H varying between 6.5 and 6.9. Another infant who was gaining properly, passed urine which in four 24 hour specimens varied from 6.1 to 6.6; four other dystrophic breast fed infants showed variations in their 24 hour specimens from P_H 6.5 to 7.4. The breast fed dystrophic infant observed by György secreted a 24 hour urine of a P_H from 6 9 to 7.6. Ylppö[410] reports the P_H of the urine of infants on simple milk mixtures as between 5.1 and 7.0. Fifteen infants fed on dilutions of cow's milk, investigated by Schloss and Harrington,[335] passed urines varying in hydrogen-ion concentration from P_H 4.8 to 6.9 with an average of 5.7. Four infants on simple milk mixtures studied by Stenström all dystrophic, excreted 24 hour urines with a P_H varying between 5.1 and 7.9. In the individual cases the daily variations were not as wide, for instance Case 8, 5.1, 5.2, 5.7; Case 10, 7.0, 7.9, 7.7, and Case 11, 6.5, 6.9, 6.7. In two infants on simple milk mixtures Shohl and Sato determined a P_H of 6.1 and 6.4. It is questionable whether the P_H of urines greater than seven given in the literature can be accepted as correct since the escape of carbon dioxide introduces an error. Under such conditions the urine must be collected under proper precautions, for instance, through a funnel dipped in paraffin oil. Marshall doubts whether urine of man ever gives a P_H greater than 8.0.[236]

Diet exercises a marked influence on the urinary reaction. For the adult Blatherwick, Blatherwick and Long, and Hasselbalch and Gammeltoft among others have given some very interesting data. Schloss and Harrington[335] lowered the hydrogen-ion concentration of the urine of an infant from a P_H of 4.8 to one of 6.3 by adding potato gruel to a diet of protein; a similar result was obtained when an infant was fed with a mixture prepared from dried milk. This illustrates the effect of adding food rich in alkaline ash to the diet. With the administration of alkali, the reaction of the urine can readily be made alkaline (to litmus). Seham gave sodium bicarbonate in doses of 0.16 gm. by mouth every two hours to newborn infants. The smallest

amount necessary to render the urine alkaline was 0.1, the largest 4.0 gm. In normal infants a single dose of from 2 to 3 gm. by mouth may be given as sufficient to render the urine alkaline and keep it so for 12 hours or more. The administration of such doses in solution by rectum is not infrequently followed by vomiting. On intravenous injection, doses of from 1 to 2 gm. are sufficient, and less time is required to produce an effect. In cases of acidosis, the dose necessary to make the urine alkaline is much greater (from about double to as much as 10 times).

It is well known that muscular activity increases urinary acidity, and that this also occurs in fever, in nephritis, diabetes, acidosis, and so forth. On the other hand increased output of water through the kidney tends to change the reaction of the urine to the alkaline side. The hydrogen-ion concentration of the urine alone cannot indicate acidosis or alkalosis, nor does it alone give any information with regard to the acid-base metabolism of the organism, or indicate the extent to which acids or alkalis are excreted through the kidney. This is easily understood when we consider that a relatively large amount of acid may be neutralized in the organism by ammonia. The ammonia salts excreted in the urine may influence the P_H little, or not at all. Under certain conditions an increased ammonia output in the urine is associated with an overflow of acid, so that Blatherwick found a correlation between the P_H of the urine and the total ammonia output. In his cases the total nitrogen output was fairly uniform. Hasselbalch finds that this condition exists not so much with regard to the total output of ammonia as to the ammonia coefficient. The greater the acidity of the urine, the greater the proportion of ammonia nitrogen in the total nitrogen. In a case of an infant, Talbot and Gamble report these figures: Ammonia coefficient 20 with P_H 5.8, ammonia coefficient 8.0 with P_H 6.1 and ammonia coefficient 7.0 with P_H 6.5. In cases reported by György and Stenström, and others, there is no distinct correlation between P_H and either the total ammonia output or ammonia coefficient. This is also true of the observations of Gamble, Ross and Tisdall,[124] who studied the effect of fasting as a therapeutic measure in epileptic children 8 to 12 years of age. There should be some correlation between the titrable acidity (or alkalinity) and the hydrogen-ion concentration of the urine, and under fairly equal conditions this is the case, as illustrated in Table 4.

Table 4.—Average Hydrogen-ion Concentration and Titrable Acidity (Henderson and Palmer)

P_H	Volume of urine, cubic centimeter	Acidity in cubic centimeter, N/10	Calculated acidity for each 100 c.c. of urine
5.4	1026	320	31
5.7	1193	303	25
6.0	1259	263	21
6.6	1400	224	16

In one of the epileptic girls, eight years of age, observed by Gamble, Ross and Tisdall such a relation seems to exist also (Table 5). Here the figures represent 24 hour averages of three day periods. During the first five periods, no food was given; during the sixth, food light in carbohydrates was taken. In the other two cases reported by these authors, this relationship is less distinct. The acidity means the number of cubic centimeters of N/10 alkali necessary to bring the urine to a P_H of 7.4, that is the hydrogen-ion concentration of blood.

Table 5.—Average Hydrogen-ion Concentration and Titrable Acidity (Gamble, Ross and Tisdall)

Period	P_H	Volume of urine, cubic centimeter	Acidity in cubic centimeter, N/10	Calculated acidity for each 100 c.c. of urine
1	5.3	817	289	35
2	5.6	1050	210	20
3	5.9	1017	119	12
4	6.0	1047	98	9
5	6.0	807	87	11
6	6.6	800	38	5

The results of Henderson and Palmer show that the relation of the P_H to the so-called titrable acidity becomes more evident when compared to the titrable acidity for each 100 c.c., that is if concentration is compared with concentration, and not concentration (P_H) with total titrable acidity, as has been done.

Obviously if dealing with the same acid in aqueous solution and at the same temperature, there would have to be a definite relationship between P_H and titrable acidity. In the urine whose acidity under normal conditions seems to be due chiefly to acid phosphates, this relationship does not always show, not even when there is no indication of any disturbance. This lack of correspondence may be due to differences of dissociation, depending on the forms in which the acid phosphate may be present, or the influence of salts on the dissociation, and on the presence of some other (organic) acids.

The total titrable acidity in the case of the breast fed infant may vary from 0 to 18 c.c. of N/10 in 24 hours,* the latter value being obtained at the time of a drop in weight. The concentration, that is, the acidity for each 100 c.c. of urine varied from 0 to 5 c.c. In the infant fed on milk mixtures, the values fall with relatively few exceptions between 43 and 128 c.c. with a concentration of 5 to 29 c.c. It is of interest to note that the infants on butter-flour mixtures (György) showed an acidity from 23 to 59 c.c. with a con-

* The figures of Lade were obtained by titrating the urine, using phenolphthalein as an indicator. His figures are therefore too high, because this indicator changes color at a P_H of about 8.3, that is, well on the alkaline side.

centration of 3 to 12 c.c. Frequently the relation of total acidity to ammonia is given under the heading of A/NH_3, the ammonia output being expressed in cubic centimeters of N/10. In the cases of Henderson and Palmer, this proportion amounted on the average to between 0.63 and 0.87. It gives in a convenient form the participation of ammonia in the total acid excretion, which is represented very well by the sum of the titrable acidity and the total amount of ammonia; both are usually expressed now in cubic centimeters of N/10.[104,159] When larger amounts of acids are ingested or formed in the organism, there is usually a corresponding increase in the formation of ammonia, the ammonia then neutralizing such acids, and permitting their excretion in the form of neutral salts. The ammonia production forms, in the words of Gamble, Ross and Tisdall, the "coarse adjustment," while the fine adjustment is left to the phosphates.* Besides ammonia the organism excretes in the urine some other basic substances, such as creatinin, and in the younger children creatin, and at times guanidins, but these play a subordinate part in the acid base regulation.

The table of Stenström furnishes a good illustration of the total acid excretion, and the difference between the urine of infants fed on human milk and on cow's milk mixtures. It represents averages of several days' observation calculated for twenty-four hours (Table 6).

Table 6.—Total Acid Excretion (Stenström)

NH_2 plus acidity*	NH_3	Titrable acidity	A/NH_3
Human milk			
40	36	4	0.11
55	46	9	0.21
75	61	13	0.23
41	35	5	0.16
32†	22	9	0.44
81‡	69	12	0.18
Cow's milk mixtures			
82	39	43	1.09
134	67	67	1.00
123	67	56	0.85
153	142	10	0.07
158	86	72	0.84

* Decimals omitted, figures mean cubic centimeters of N/10.

† Poor gain in weight, otherwise normal.

‡ Normal. All other children dystrophic.

* Recently Berg denies the possibility of the presence of monometal phosphates in complicated body fluids, or in urine as long as these fluids react alkaline to Congo ($P_H = 5$). But this indicator has a big salt error.

For a dystrophic breast fed infant, György gives an average of $NH_3 + A = 55$, $NH_3 = 53$, $A = 2$ and $A/NH_3 = 0.04$, and for a normal infant fed on milk mixture $NH_3 + A = 145$, $NH_3 = 77$, $A = 68$, and $A/NH_3 = 0.88$, while another normal infant fed on butter-flour milk gave $NH_3 + A = 132$, $NH_3 = 101$, $A = 31$, and $A/NH_3 = 0.31$.

Vozarik determined the acidity of the urine in three boys, nine to ten years of age, on various forms of diet in ten-day periods. His results are summarized in Table 7.

TABLE 7.—ACIDITY OF THE URINE (VOZARIK)

	NH_3 + acidity*	NH_3	Titrable acidity	A/NH_3
Vegetarian diet				
A	424	233	191	0.82
B	458	270	182	0.67
C	537	272	205	0.75
Mixed diet				
A	467	265	202	0.76
B	550	326	224	0.69
C	573	303	270	0.89
Meat diet				
A	647	360	287	0.80
B	704	434	270	0.63
C	622	362	260	0.71

* The acidity was determined, using phenolphthalein as indicator. The figures are, therefore, too high.

All diets were really mixed diets, the first furnishing about 1.7 gm. protein for each kilogram (total 40 gm.), the second 2.9 gm. for each kilogram (total 71 gm.), the third 4.5 gm. for each kilogram (total 109 gm.). It is evident that diet influenced the total acidity of the urine, increase of protein tending to increase urinary acidity.

How the conditions are changed on fasting are illustrated by the figures given by Gamble, Ross and Tisdall[111] in the case alluded to above (Table 8).

TABLE 8.—EFFECT OF FASTING ON THE ACIDITY (GAMBLE, ROSS AND TISDALL)

	Period	NH_3 + acidity	NH_3	Acidity	A/NH_3
Fasting	1	891	602	289	0.48
	2	1122	912	210	0.23
	3	877	758	119	0.16
	4	628	530	98	0.18
	5	533	446	87	0.20
Carbohydrate diet	6	274	236	38	0.25

The two other cases also, with periods of fasting of ten and four days showed a marked drop of ammonia and titrable acidity on resumption of feeding.

As Folin pointed out, the determination of acid phosphates besides that of the titrable acidity indicates the amount of organic acids participating in the titrable acidity. An ingenious method for the determination of organic acids excreted in urine (the sum of free and combined acids), has been introduced by Van Slyke and Palmer. Urine is titrated between hydrogen-ion concentrations represented by $P_H = 8$, and $P_H = 2.7$ after removal of phosphates and carbonates with calcium hydroxid. The titration represents between 95 and 100 per cent of the organic acids present. Corrections have to be made for certain weak bases, but of these only creatinin and creatin enter into consideration. Corrected for creatinin, thirteen young men excreted from 240 to 600 N/10 acid in the form of organic acids in twenty-four hours with 4.7 to 9.6 c.c. for each kilogram, or on an average about 6 c.c. for each kilogram of body weight (uncorrected, 8 to 11 c.c.). In the cases of Gamble, Ross and Tisdall, the organic acids increased very decidedly during the fast, due to the increase of keto acids. In the first case, after resumption of carbohydrate feeding, the organic acids, after correcting for creatin and creatinin, dropped from 857 c.c to 131 c.c. This eight year old girl had an average weight of 22.7 kg. for the whole period of the experiment. The second case, a girl 12 years of age, excreted 166 c.c. in the fore-period; during the fasting this rose to 1009 c.c., and varied in the seven-day after-period on standard diet from 141 to 186 c.c. The third case, an eight year old boy, excreted 146 c.c. in the fore-period, during the four-day fast as much as 837 c.c., and on resumption of carbohydrate feeding the value dropped on the second day to 144 c.c.

The figures given by Utheim for normal infants, one to twenty months of age, are 7.2 (?) to 12.8 c.c. for each kilogram of body weight with a total of about 26 to 81 c.c. These figures are apparently not corrected for creatinin and creatin. In only a few cases of different ailments, figures less than 5 c.c. for each kilogram of body weight are recorded, one of these in athrepsia. In other cases of parenteral and enteral infections, as well as in athrepsia, the excretion of organic acids was increased. In 49 of 61 determinations in ten cases of athrepsia, more than 15 c.c. for each kilogram of body weight was excreted with a maximum of 58 c.c. for each kilogram and 190 c.c. total. In the cases of athrepsia the magnitude of the ammonia excretion was in a general way proportional to that of the organic acids, this parallelism, however, being by no means constant.

Albuminuria.—The question of whether or not normal infants' urine contains protein has been discussed by numerous authors, particularly with reference to the newborn. Czerny and Keller give a detailed account of this discussion. They do not accept the albuminuria of the newborn as a physiologic phenomenon, because neither the influence of nutrition, nor its disturbances, have been sufficiently

considered in relation to its occurrence. It is undoubtedly of importance to know whether a normal newborn excretes a urine which contains protein. But it is very difficult to decide what constitutes the normal for a newborn infant which has been exposed at birth to more or less traumatism, as a rule associated with a greater or lesser degree of asphyxia. During the first week of life the loss of weight occurs. This loss was regarded as physiologic until Schick showed that it need not occur. The question, then, is not so much whether the albuminuria occurs in strictly normal newborn infants, but whether the albuminuria observed in the majority of newborn infants is of clinical significance. This much is generally conceded, that the urine of most newborn infants does contain protein at some time during the first week of life. This statement rests on the fact that, on the addition of acetic acid to urine in the cold, a more or less pronounced turbidity occurs, leading to the formation of a precipitate on standing. The nature of this protein is not known. It has been regarded as a mucin, as is but natural, being precipitable by acetic acid. Some speak of it as nucleoprotein for want of a better term. Mörner believed the protein found in normal adult urine to be serum protein. This is not precipitable by acetic acid in the cold. The fact that a precipitate is obtained in this manner is explained by the presence of chondroitin sulphuric acid in urine. The acetic acid is supposed to liberate the chondroitin sulphuric acid from a combination, so that it can react with the protein. Chondroitin sulphuric acid precipitates protein in high dilutions. Adding horse serum to the urine of the newborn Franz and von Reuss very frequently obtained positive reactions showing that the urine contains a protein precipitating substance.

The results which Doerr and Pick obtained with precipitin tests do not support the view that the protein in normal adult urine is serum albumin, but point to the kidneys as its source. In the animal experiment a kidney perfused with a solution containing no protein can produce a secretion containing protein.[172] But these are very unusual conditions.

While most observers agree that the urine of the majority of newborn infants contains a trace of protein at some time during the first week of life, there is marked disagreement with regard to certain phases of the problem. This may be illustrated best by two reports. Heller examined the urine of 48 infants at birth, and found in only two instances minimal traces of protein. Franz and von Reuss examined the urine voided within a few minutes after birth and found minimal traces of protein in twenty of 39 cases. Heller found protein precipitable by acetic acid, in the urine of 31 infants, at least once during the first week. There was also another protein precipitable by acetic acid and potassium ferrocyanide in 29 of the 31 cases. The collection of 24 hour specimens served for his tests. Franz and von Reuss examined single specimens of 70 newborn infants during the first week of life, not always daily, and not always for the whole week. A few of the infants were not in the best of health. These

authors agree with Heller that the acetic acid precipitable protein is most common during the first three or four days, in about 78 per cent. of their cases, but they found present only rarely the other protein precipitable by acetic acid and potassium ferrocyanide. They agree with Heller that protein is not demonstrable after the first week, and that it is an albuminuria minima.

From these observations it is evident that no particular clinical significance attaches to these findings. It cannot be accepted as quite certain that this protein precipitable by acetic acid is always absent from the urine after the first week of life. It may be that the dilution of the infant's urine makes the tests less reliable. Giffhorn found the protein not infrequently in infants' urine, but regards its occurrence as a very sensitive indicator of various disturbances. Hamill and Blackfan examined the urine of 124 children whose ages varied from eighteen months to fourteen years. The albuminous body precipitable by acetic acid in the cold was demonstrable in about 85 per cent. of these children. In about 27 per cent. another protein (serum albumin) was present, either alone or in association with the first, bringing the total of the positive reactions to about 89 per cent. These proteins were nearly always present in very slight traces. In 38 cases 24 hour specimens of urine were examined. Only in one of these no protein was found, and single specimens examined later in the same case, gave a positive test. In 16 of these cases, serum albumin was also demonstrable. Hamill and Blackfan express the belief that it is possible to demonstrate in the urine of every presumably healthy child traces of an albuminous body precipitable by acetic acid. Its presence is devoid of clinical significance. Serum-albumin in the amounts found is no more an indication of disease of the kidneys than the occasional presence of hyaline casts and cylindroids.

The peculiar condition in which protein is excreted in the urine when the individual rises from a recumbent to the erect position goes under the name of orthostatic albuminuria. It is most common in later childhood up to the age of puberty. Although the urinary findings are the only features having a just claim to consideration here, certain other phases of orthostatic albuminuria deserve passing mention. One of the main difficulties is the decision as to whether or not any permanent renal lesions are lurking in the background. In one case of Heubner's, necropsy was made. No lesions of the kidneys could be demonstrated. Nevertheless Pollitzer, for reasons to be taken up later, insists that some lesion of the kidney is very probable. Jehle defends his theory that the causative factor is an arc-like lordosis, whose maximal point of deviation falls in the region of the first and second lumbar vertebra. This lordosis produces a renal venous stasis, which in turn is responsible for the lordotic albuminuria. In his cases such a lordosis was either constantly visible, or occurred with certain postures which also elicited the albuminuria. Furthermore, he was able to provoke an albuminuria in the recumbent position in cases of orthostatic albuminuria, as well as in normal persons, by pro-

ducing a lordosis, or by pressure on the vena cava. When a pronounced lordosis is sustained for a longer period in such experiments, it may lead to the appearance of casts and red blood corpuscles in the urine. In spite of this, no discoverable trace of lasting renal lesion remains. For such reasons Jehle justly regards the occasional appearance of these elements as compatible with a real orthostatic albuminuria for which he introduces the term "lordotic albuminuria." Another strong argument in favor of Jehle's theory is the fact that correction of the lordosis made the albuminuria disappear. Jehle advances many good reasons in support of his theory that lordosis is the only factor concerned in the production of this form of albuminuria. Nevertheless there are some reasons militating against the acceptance of this view without reservations. Götzky claims that there are cases of orthostatic albuminuria without lordosis, and that there are cases of marked lordosis without orthostatic albuminuria, even though the maximal deviation falls on the first and second lumbar vertebra. Jehle explains the diminution of albuminuria during the afternoon on the basis of increased efficiency of the collateral circulation. But this can hardly explain the diminution of the albuminuria following the ingestion of a meal, as seen by Erlanger and Hooker. Jehle was eminently successful in preventing the albuminuria by correction of a lordosis, but other procedures can bring about cessation of the albuminuria. The experiment of Erlanger and Hooker, exercising pressure on the lower extremities by means of a pneumatic suit* and thereby diminishing the albuminuria, is very suggestive. Furthermore, immersion in water in the upright position diminished or prevented the occurrence of the albuminuria provided the water was tepid or hot, while immersion in a cool bath did not diminish the orthostatic albuminuria, or only slowly. Erlanger and Hooker found a relationship between the amplitude of the pulse pressure and the occurrence or the degree of the orthostatic albuminuria, the amplitude being smaller in the albuminuria.

The albuminuria in the few observations of Mason and Erickson varied inversely with the pulse pressure, but in the 26 cases studied by Bass and Wessler, this relationship did not stand out prominently. Whether or not lordosis is the only factor responsible for the circulatory changes in the kidneys, circulatory changes in the kidneys are responsible for the appearance of the orthostatic albuminuria. This view is strengthened by the observations of Sonne. When catheterizing the ureters in a lordotic position, there occurred an oliguria and albuminuria on the left side only, both disappearing with correction of position. One of the patients of Rieser and Rieser, whose right kidney had been removed, had very pronounced oliguria and albuminuria. In both of their cases, correction of the visceroptosis without correction of the orthostatic posture and without significant difference in the pulse pressure, led to the disappearance of the albuminuria. The peculiar anatomic position of the left renal vein exposes it to pres-

* The suit reaches the iliac crests and takes in part of the abdomen apparently.

sure from the aorta pushed forward by the lordotic spine, or to pressure exercised by the aorta and superior mesenteric artery, brought about by visceroptosis.

This, however, does not determine whether the kidneys of the orthostatic person are absolutely normal.

The main interest in the urine centers in two of its properties; the appearance of protein, supposedly from the blood serum, under the conditions discussed, and the ability of the urine to give a precipitate on the addition of acetic acid. As pointed out, the mechanism of the reaction is supposed to depend on the liberation of chondroitin sulphuric acid, which combines with the protein which may be present in the urine. The urine voided by the orthostatic child when in an erect position often gives a more pronounced reaction on addition of acetic acid, than on boiling. But urine voided in a recumbent position, although free from protein and not giving a reaction on the addition of acetic acid, was found by Pollitzer to contain the protein-precipitating substance, for on addition of acetic acid and serum a precipitate was obtained. He observed the occurence of the acetic acid precipitate in the course of certain infections, particularly tonsillitis and angina. He attributes the orthostatic albuminuria to chronic tonsillitis with repeated exacerbations, which need not become noticeable clinically. The excretion of the protein-precipitating substance, a condition which he calls chondroituria, is the manifestation of a lasting injury to the kidneys. Traces of this adialysable chondroitin sulphuric acid are supposed to occur in urine normally, so that chondroituria means an excretion exceeding normal. Pollitzer, in discussing the kidneys of infants, uses changes in the specific diuresis and the chondroituria as means to distinguish orthostatic albuminuria of the type associated with lesions from that due to static neurosis. Schippers and de Lange deny that chondroituria indicates a renal lesion, and do not find it characteristic for orthostatic albuminuria; this is the prevailing opinion.

On standing erect the person with orthostatic albuminuria, like the normal person, excretes less urine than in the recumbent posture. Expressed in per cent. of the amount excreted in a recumbent position, Erlanger and Hooker found on an average 67 per cent. nitrogen excreted by the normal person on standing, and 56 per cent. by the orthostatic person, without allowing for the protein excretion in the latter. The phosphates and chlorids were also more diminished in the orthostatic person, while the water output was less diminished. Jehle also reports a chloride retention with the appearance of the albuminuria. This retention may be only very transitory, or it may last an hour, or an hour and a half. The chloride excretion then increased independently of the existing albuminuria. In cases with longer retention of chlorids, cylindruria may occur later. Oliguria, chloride retention and cylindruria disappear on reclining. In cases in which the albuminuria was provoked by an extreme lordosis of short duration, the chloride retention occasionally preceded the albuminuria.

Götzky obtained the urine of a child in the lordotic position by catheterization of the ureters, and found in the urine of both sides numerous oxalate crystals, but the amount of oxalic acid excreted by the orthostatic person does not seem to be different from that excreted by normal persons.

Of the greatest interest is the fact brought out by Nassau[272] that the administration of alkali with the production of an alkaline urine relieves the orthostatic albuminuria in the majority of cases without any further procedures. Nassau explains this result by assuming the correction of a process in the kidney due to stasis.

The orthostatic albuminuria may associate itself with other symptoms, which have been ascribed to faulty body mechanics.

In some cases of orthostatic albuminuria, with the occurrence of the albuminuria, an alimentary galactosuria was found by Maliwa. In some cases of Beckmann and Schlayer the orthostatic albuminuria yielded to the administration of atropin, and was regarded as intimately associated with vagotonia. Saito considers a large majority of them in the state of vagotonia. The painstaking investigations of Friedberg with regard to the pharmacologic tests of the vegetative nervous system in childhood make even the possibility of an establishment of vagotonic or sympathicotonic states very questionable.

Under certain conditions it is possible to demonstrate protein derived from food in an infant's urine. The proof of such an occurrence has been brought by means of biologic methods, such as the precipitin reaction with a specific antiserum, or with the anaphylactic test in the guinea pig. Most of the positive results were obtained on adding egg white to the diet of infants. The results of Lawatscheck indicate that if egg white is given during the first ten days of life, the urine often contains albumin. These observations were confirmed by Grulee and Bonar. Later on, this may occur occasionally in infants free from gastro-enteric disorders. Lust[221] found albumin once in a perfectly healthy, breast fed infant on the addition of the white of two eggs to the diet; for this reason he did not exceed this dosage in his cases. Schloss and Worthen found a positive precipitin test in two cases free from gastro-enteric disorders, after adding the white of one and one-half, or of two eggs to the diet. Lust further found that in infants with gastro-enteric disorders, the albumen could be more frequently found in the urine than in normal infants, and that the more frequently it was found, the more severe was the disorder. The results of Lust were confirmed by Schloss and Worthen, who added the observation that egg albumen may pass in the urine of eczematous children. Furthermore, they found in two cases of acute gastro-enteric disorder a positive precipitin reaction with cow's lacto-antiserum, showing the passage of cow's milk protein in the urine. Like Lust they found the precipitin reaction more sensitive than the anaphylactic test. It is of interest that the passage of beef protein (beef juice or serums) given by rectum could only be demonstrated in one of Lust's seventeen cases (gastro-enteric disorders), a result

the more remarkable as some of these infants had passed some egg albumen. The protein derived from the food passes in the urine only in very small quantities, if at all. Older children free from nephritis may pass protein if fed large amounts of raw eggs. In Kaliski and Weigert's case of nephritis in which this happened, it was not determined whether the protein came from the egg. The results of Hecker and of Hayashi contrary to those of Krasnogorski seem to show that in cases of albuminuria, protein foreign to the ogranism may pass in the urine. Hayashi tested the urine of thirty children one-half to twelve years of age. The urine of nine of the children (one and one-half to eleven years of age) gave a positive reaction when tested with antiserums of high titer. Four passed egg proteins, and five urines reacted to cow's lacto-seulm. One cannot help but feel somewhat uncertain about these latter results because a similar reaction was not obtained with anti-cattle serum.

Nitrogen.—According to Michel it would appear that the nitrogen excretion, in relation to the intake, for the first days of life, is very small, and that more nitrogen is retained than later on. These figures are open to serious criticism. Nevertheless, in a case of Schloss and Crawford, the retention during the first three days of life was about 33 per cent., and during the next six days about 63 per cent. In another case the nitrogen retention was about 51 per cent. during the first three days of life, and during a period comprising the third to seventh day of a premature infant, Schwarz reports a retention of 79 per cent. Orgler[283] found a retention of about 40 per cent. in infants of two to three months, of about 23 per cent. in those of five months. From the end of the first month of life to an age of five months, the nitrogen retention varied from about 30 to 58 per cent. in healthy, breast fed infants. [16,214,233,268,347] The number of observations during the first two months of life is too small for the definite statement that the nitrogen excretion increases gradually. Roughly the nitrogen excretion in the urine of the breast fed infant, under usual conditions, may vary between approximately 65 and 90 per cent. of the excretion in urine and feces.

In health, the extent of the total nitrogen excretion in the urine is mainly dependent on the amount of nitrogen taken in with the food, provided the food is properly balanced. During the first few days of life the nitrogen excretion in the urine may exceed the intake.[49, 206, 359, 373] It is not quite certain whether this is a constant occurrence. In some cases reported in the literature in which the urine of several days was used collectively, a positive nitrogen balance was recorded. Indeed Birk,[47, 48] examining a newborn infant fed with colostrum, found a positive nitrogen balance in spite of a drop in weight, and Schloss and Crawford found the same in two cases.

Expressing the amount of nitrogen retained in per cent. of the intake, Orgler gives for an age of 14 days about 78 per cent. (a figure to which Lindberg takes exception), for two to three months about 40, and for five months about 23 per cent. Mueller gives the result of

metabolism experiments in 32 children from two to six years of age. In 28 of these the nitrogen balance was positive. In none of these cases did the retention ever reach 20 per cent. Stargardter records observations on three boys five and three-fourths, six and two-thirds, and seven and three-fourths years of age. The nitrogen retention varied from 8.2 to 10 per cent. The average retention of the six boys observed by Herbst, whose ages varied from six and one-half to fourteen years, was 11 per cent. The material on which these figures are based is not as comprehensive as could be desired. The differences between the individual determinations is rather wide. In all of these cases the food was actually analyzed. The retention of nitrogen is not solely dependent on the nitrogen intake, but also on the relation of the nitrogenous to the non-nitrogenous food. It is well-known that carbohydrates favor nitrogen retention. An experiment of Stargardter is of special interest. One boy served for all the observations. Various sugars were given in equal amounts, while the rest of the diet remained the same. The sugars were lactose, glucose, maltose, and cane sugar. The retention of nitrogen following this arrangement was 3.7, 5.0, 5.9, and 5.6 per cent. The highest retention was obtained with maltose, the lowest with lactose.

In the calculation of the retention, the nitrogen excreted in the feces is taken into consideration. It is quite possible that the same child at different periods may show quite marked fluctuations, so that even periods of negative nitrogen balance may occur, such as Camerer has described in his children. The phenomenon of the increased nitrogen excretion with advancing age might perhaps be brought in relation with the rate of growth. And this rate of growth need not be uniform.

Since a normal infant excretes very little nitrogen in the feces when exposed to hunger, the nitrogen content of the urine in hunger may be taken as a measure of the decomposition of body protein. It had been known that the minimal protein requirement of the adult man and of animals on a properly balanced diet is less than the amount of body protein which is used up in hunger. Amberg and Morrill,[16] Vogt, Schlossmann and Murschhauser showed that the infant does not behave differently. To the latter authors we owe most of our information concerning the hunger metabolism of infants. They found that the previous diet of an infant influences its nitrogen excretion during hunger. If the diet contained much protein, more nitrogen is excreted during hunger than if it contained little protein. The artificially fed infant excretes more nitrogen during hunger than the breast-fed. An infant within its third month of life fed with human milk excreted in the urine 3.6 mg. nitrogen for each kilogram of body-weight each hour. On the first hunger day it excreted 5.1 mg., on the second 6.8 mg., and on the third 10.8 mg. On one-half milk with addition of flour, the same infant excreted 11.5 mg. for each kilogram each hour. On the first hunger day it receded to 15.1 mg. It was observed in other cases also that the breast fed infant increased its nitrogen output on successive days of hunger while the artificially fed infant decreased it after

the first hunger day. Schlossmann and Murschhauser conclude from their observations that the breast-fed infant can withstand hunger more readily than the artificially fed. Whether all these distinctions between the breast and artificially fed infants will stand must be determined by further observations. It is not surprising that the organism uses up more of its body protein in hunger than it requires for maintenance, or even for some growth, on a diet poor in protein if no more than the insufficient supply of carbohydrate is considered. Edelstein and Langstein arrive at the minimal protein requirement of infants by the determination of the nitrogen output on a diet practically free from protein, but calorically sufficient. For infants in the first half year of life, the average nitrogen elimination is given as 0.448 gm. in 24 hours. Of this nitrogen 0.298 gm. or about 67 per cent., was excreted in the urine. As a rule, the nitrogen excreted in the urine exceeds considerably the nitrogen excreted in the feces. Von Müller averages the excretion of nitrogen in the urine at about 80 per cent. of the intake in children past infancy, who are on a liberal protein diet.

Under pathologic conditions, such as febrile diseases, atrophy, and athrepsia, the excretion of nitrogen in the urine may exceed the nitrogen in the food. In some cases of athrepsia, Utheim found that the nitrogen balance was negative when the infant gained weight.

On the whole, the infant holds on to its nitrogen with great tenacity. It has been seen repeatedly that a marked loss of weight was associated with a positive nitrogen balance. Somewhat similar observations have been reported in older children.

No figures have been given for the total excretion of nitrogen in the urine, because it is dependent on a variety of factors. Without a discuss on of these factors, figures would be meaningless and a proper discussion would lead too far into the realms of metabolism. For the same reason figures for the total excretion of urea, the most abundant of the nitrogenous urinary constituents, are omitted.

Urea.—In the adult under usual conditions of nutrition, that is, a diet rich in protein, urea forms a rather constant part of the urinary nitrogen. On a decidedly reduced nitrogen intake, urea forms a smaller percentage of the total nitrogen (Table 9).

The greatest reduction in the percentage of urea nitrogen is not found in hunger, but on a low protein diet (Cathcart). Robison reports urea nitrogen as low as 37 per cent. The share of the urea nitrogen in the total urinary nitrogen of supposedly normal infants shows very wide variations. Vogt remarked very justly that such wide variations could hardly occur without special reasons. The divergent results of earlier authors are probably due in part to differences in the methods employed for the urea determinations. A number of observations are made on infants who were too abnormal. In other cases the diet was not controlled analytically with that degree of accuracy which is necessary when debated questions are to be decided. The whole problem of the nitrogen partition in the infant's urine needs revision. The latitude of the norm is not fixed by a

TABLE 9.—THE SUMMARY OF FOLIN[105]

Food	Total nitrogen, grams	Urea nitrogen, per cent.	Ammonia nitrogen, per cent.	Uric acid nitrogen, per cent.	Creatinin, per cent.	Undetermined, per cent.
Protein 118 gm. = 19 gm. of nitrogen. Fat 148 gm. Carbohydrate 225 gm.	16.8	89.5	3.0	1.1	3.6	4.9
Protein 6 gm. = 1 gm. of nitrogen. Fat 52 gm. Carbohydrate 400 gm.	3.6	61.7	11.3	2.5	17.2	7.3

sufficient number of determinations correctly made. Under these conditions a few data may be given chiefly for the purpose of indicating the status of the problem. For the earlier period of infancy Simon[359] reports results obtained in four cases in which the infants were fed with human milk from the bottle. The food was analyzed. The urea was determined by the method of Sjöquist (Table 10).

TABLE 10.—UREA NITROGEN, PER CENT. OF THE TOTAL URINARY NITROGEN (SIMON)

Case	Day of life													
	1 and 2	2	3	4	5	6	7	8	28	29	34	36	46	47
1	73.8		69.1	65.8	65.8	58.5	70.1							
2			92.9		65.2			66.8	65.0	64.6				
3		57.9		53.1			58.5						60.4	71.0
4		67.7		63.5			72.3				67.2	55.7		

Case 1. Weight 3020 gm. on the first day and 2950 on the eighth.
Case 2. Weight 2470 gm. on the third day, 2540 on the ninth, and 2740 gm. on the twenty-eighth.
Case 3. Weight 2900 gm. on the second day, 2620 on the eighth, and 3280 on the forty-sixth.
Case 4. Weight 2840 gm. on the second day, 2770 on the eighth, and 3120 on the thirty-fourth.

Such infants can hardly be regarded as representatives of well developing breast fed infants.

Vogt used the method of Folin. His results were obtained on infants free from gastro-intestinal disorders. Further data are not

given. The diet consisted of breast milk, but it was not analyzed (Table 11).

TABLE 11.—ANALYSIS OF URINE IN BREAST-FED INFANTS (VOGT)

Name	Age, weeks	24-hour urine		Total nitrogen, milligram	Urea nitrogen		Ammonia nitrogen		Rest nitrogen	Amount of breast milk, gram
		Centimeter	Per cent. of intake		Milligram	Per cent. of total nitrogen	Milligram	Per cent. of total nitrogen		
Gr....	4	152	30.4	239.7	75.92	31.68	70.2	29.29	39.03	500
	8	489	58.2	545.9	394.3	72.23	37.42	6.86	20.91	840
	12	587	74.3	596.5	392.0	61.73	58.98	9.73	28.54	790
	15	529	66.4	599.6	288.5	48.1	91.35	15.07	36.83	800
Schw.	8	260	41.3	302.8	165.4	53.65	32.03	10.39	35.96	630
Fra...	5	237	39.5	551.6	295.1	53.51	70.48	12.77	33.72	600
Bin...	9	170	34.0	288.8	174.96	60.59	24.25	12.13	27.28	500
Ju....	14	305	50.8	414.1	252.5	63.46	39.8	9.61	26.93	600

In the case of infant Gr., aged four weeks, and of Bin., no explanation is offered for the extraordinarily small urine secretion.

For an infant five and one-half months old and one, one year old, both breast-fed, Camerer gives 79 and 75.5 per cent. urea nitrogen.

The infant observed by Talbot and Gamble was five and one-fourth months of age. In the first period, on a diet containing 2.3 gm. protein for each kilogram of body weight each day, 62.5 per cent. of the urinary nitrogen was excreted in the form of urea. In the later periods 4.4 and 4.8 gm. of protein for each kilogram were given. The urea nitrogen rose to 83.8 and 83 per cent. In the first period the baby, which was considerably underweight, did not get sufficient food to permit good progress.

In normal infants Meyer and Rietschel[254] ascribed 60 to 80 per cent. of the nitrogen to urea.

In children 19 months to 12 years of age, fed on a standard diet with a liberal allowance of protein, the urea determined by the urease method contained from 78.5 to 87.7 per cent. of the urinary nitrogen. Johnston and Veeder, who furnished these data, conclude that the sum of the nitrogen contained in urea and ammonia constitutes somewhat less than 90 per cent. of the urinary nitrogen of children, while in the adult it is as a rule over 90 per cent.

Ammonia.—It is self evident that a variation in any of the nitrogenous constituents of the urine must influence the nitrogen percentage of the others. Such a relationship is perhaps most strikingly shown between urea and ammonia. A marked increase in ammonia is always reflected in a decrease of urea. The ammonia is derived from nitrogen of the proteins, which is also the source of urea. Depending on conditions, more or less of the nitrogen is excreted as urea or ammonia. It has long been known that certain ammonia salts, when

injected in animals, are excreted as urea. But the experiments of Nash and Benedict suggest that urea may be the source of ammonia and, furthermore, that ammonia is formed in the kidney. Of interest are the results of Keeton, in which ammonia output and ammonia coefficient increased definitely on the administration by rectum, of hydrochloric acid, while on intravenous injection total nitrogen and ammonia excretion increased, so that the normal ammonia coefficient was fairly well maintained. Keller[186] was the first to call attention to the increase of ammonia nitrogen in severe gastro-intestinal disorders of infants. Hereby the total amount as well as the ammonia coefficient was increased. The ammonia coefficient means the ammonia nitrogen expressed in per cent. of the total nitrogen. Czerny and Keller soon found that the diet exercised a definite effect on the ammonia excretion and that it was particularly the amount of fat which entered into consideration. These observations and the part the ammonia plays in the acid base equilibrium of the organism would make it very desirable to have the normal of the ammonia coefficient established on a better foundation. As has already been said, it is dependent on the diet. Folin (Table 9) shows that in the adult it increases on a low protein diet. With marked diminution of the protein metabolism leading to a decrease of nitrogen in the urine, there is usually, though not always, a decrease of the absolute amount of ammonia in the urine. A marked diminution of the total nitrogen is always associated with a relative increase of the ammonia nitrogen, provided the food does not leave an alkaline ash. Meyer and Langstein claim that in normal infants the ammonia coefficient rarely exceeds 10 per cent. Czerny and Keller cite the data of Simon[359] as an example of young infants fed on human milk and doing well, "During the first days of life the ammonia coefficient is as a rule lower than at the end of the first week, as is stated, when it reaches rather high values, on an average about 15 per cent., and this seems to be common in breast-fed infants." It has been pointed out that the infants studied by Simon do not measure up to standard.

The ammonia coefficient of about 29 per cent. obtained by Vogt is very questionable (Table 11).

Two cases given by Meyer and Langstein show an increase of the ammonia coefficient during fasting; in one case it rose from 7.6 per cent. to 17 per cent. on the second day, and to 25 per cent. on the third day; in the other from 3.4 per cent. on the first day to 26 per cent. on the third day. In cases reported by Vogt, two days on a tea diet did not produce any very marked difference; neither was the influence of hunger very marked in the case of Amberg and Morrill.[16] The divergent results recall the statement of Cathcart that in adults the increase in ammonia nitrogen in hunger may be delayed for several days. In two of the cases of Gamble, Ross, and Tisdall, the ammonia coefficient increased definitely on the third day.

Table 12 from Czerny and Keller shows the influence of diet, particularly of fat (case not normal).

The results of Hoobler were obtained on an infant nine months old. It was fed on milk mixtures prepared from whole milk, fat free milk, and 16 per cent. cream without the addition of carbohydrate. The low fat diet contained 27.3 gm. fat, and 53.3 gm. protein; the medium fat diet, 51.2 gm. fat, and 44.8 gm. protein, and the high fat diet, 72.2 gm. fat and 44.3 gm. protein, which means for the last period over 5 gm. protein for kilogram of body-weight each day. The fat for each kilogram each day was 3.6 gm., 6.4 gm. and 9 gm. respectively. After keeping the baby on one of the diets for two days the collection of urine was started and continued for a period of three days (Table 13).

In this case, a normal infant, the ammonia coefficient increased with the increase of the fat in the diet, but it was less on the high fat diet than on the medium fat diet. In all periods the urea nitrogen changed abruptly on the second day, and so did the ammonia coefficient, particularly in the second period. This is really the fourth day on which the infant was on the particular diet. Either an unknown factor, aside from the change in diet, entered into consideration, or it takes some time to bring out the influence of the change in diet.

In the older children studied by Sawyer, Stevens and Baumann the greatest increase of ammonia output did not occur immediately on the change to a high fat diet. A low caloric, acid-producing diet also increased the ammonia output as did the acid diet of Baumgaedt.

In a breast fed infant, about one month old (taking about 2.3 gm. protein and 7 gm. fat for each kilogram of body-weight each day), Amberg and Morrill[16] found an ammonia coefficient of about 8 per cent. On a modified human milk with about 0.7 gm. protein and 4.7 gm. fat for each kilogram each day the ammonia coefficient rose to about 20 per cent. From these results, as well as from data reported in the literature, the conclusion was reached that the ammonia coefficient depended within certain limits not so much on the absolute amount of fat in the diet as on the relation of fat to protein. With an increase of the ratio $\frac{F}{P}$, the ammonia coefficient tends to increase. In this case the diet low in protein and relatively rich in fat was given following a period of hunger, during which the ammonia coefficient had risen but little. Neither during the hunger period, nor during the later periods did the actual amount of ammonia vary greatly from the initial period.

The three infants of Courtney and Moore, seven to eight months old, received a diet extraordinarily rich in protein. In these cases a rise of temperature occurred. The ammonia coefficient rarely exceeded 5 per cent., and never reached 10 per cent. The normal infant of Noack had an ammonia coefficient of 11 and 14 per cent. on a milk mixture, in which the protein content exceeded the fat content. With an increase in fat to more than three times its amount, the ammonia coefficient rose to 16 and 19 per cent., with a ratio of protein to fat not exceeding 1:2.3. The observations of Talbot and Gamble concern an infant not measuring up to normal, with a ratio of protein

TABLE 12.—INFLUENCE OF DIET ON AMMONIA EXCRETION (CZERNY AND KELLER)
Case II. Age at beginning of examination: two months

Date	24-hour urine, centimeter	Total nitrogen, milligram	Ammonia nitrogen		Food contains		Kind of food
			Milligram	Per cent. of total nitrogen	Protein per cent.	Fat, per cent.	
March 3	225	315.0	53.55	17.0	0.86	3.6	
6	260	364.0	87.36	24.0	0.86	3.6	
10	440	662.2	104.72	15.8	0.86	3.6	Cream
13	376	500.08	168.45	33.7	0.9	5.7	
17	318	601.02	133.56	22.3	0.9	5.7	
21	500	735.00	131.00	15.0	0.9	5.7	
25	460	2543.8	128.8	5.1	3.4	0.1	
28	460	2704.8	83.72	3.1	3.4	0.1	
30	530	2893.8	44.52	1.5	3.4	0.1	Skimmed milk
31	395	2433.2	44.24	1.8	3.4	0.1	
April 2	585	2866.5	66.52	2.3	3.4	0.1	
3	510	2677.5	55.08	2.7	3.4	0.1	
9	550	654.5	100.1	15.2	0.9	5.9	
10	515	721.0	108.15	15.0	0.9	5.9	
11	430	421.4	84.28	20.0	0.9	5.9	Cream
13	420	441.0	70.56	16.1	0.9	5.9	

TABLE 13.—THE NITROGEN OF UREA AND AMMONIA IN PER CENT. OF THE TOTAL NITROGEN (HOOBLER)

	Urea nitrogen, per cent.	Ammonia nitrogen, per cent.
First period	76.0	2.5
	89.8	3.7
	89.8	3.7
Second period	81.5	3.6
	58.0	33.3
	49.6	38.3
Third period	87.2	5.5
	45.8	118.5
	58.1	30.5

to fat of 1:3.6, the ammonia coefficient was 20 per cent.; with a ratio of protein to fat of 1:1.8, it dropped to 8 per cent., and with one of 1:1.5, it was 7 per cent. The total ammonia nitrogen averaged for the first period 195 mg., for the second, 156, and for the third, 175 mg. In the three dystrophic infants of Howland and Cooke, an increase of the ammonia coefficient was also noted on an increase of the fat in the food, particularly when the fat exceeded the protein. But

in one of these infants, which tolerated fat very well, the ammonia coefficient dropped again on the highest fat ration, with a change of the proportion of protein to fat from 1:2.3 to 1:3. This latter proportion is by no means excessive. This observation recalls the observations on fasting individuals where the total ammonia excretion and ammonia coefficient may decrease again as fasting progresses. But besides emphasizing individual differences, such observations illustrate that in the evaluation of one factor or set of factors, due caution must be exercised. Niemann[276] added fat to the diet of five infants. Three had rachitis. These responded with a greater increase of ammonia excretion than the two normal infants. The increase of the urinary ammonia became much more pronounced when the carbohydrates of the food were reduced considerably. This is in keeping with numerous observations of the effect of so-called ketogenic diets. Unfortunately, Stenström does not give more exact data about the composition of the food in his experiments. A number of infants were fed human milk freed from fat with the centrifuge, to which sugar had been added. This led to a more or less pronounced increase of the ammonia coefficient, and in some cases, including two normal infants, to an increase in the total ammonia output, in spite of a diminution of the total nitrogen excretion. In the dystrophic infants receiving whole milk mixtures, the addition of cream in place of some of the sugar, led to a moderate increase of the ammonia coefficient, and in three out of four, to an increase of the total ammonia, together with a decrease of the total nitrogen.

That a diet relatively rich in carbohydrate can be associated with an increased ammonia output has been pointed out by Keller.[187] It must be acknowledged that the influence of diet on the ammonia excretion and the ammonia coefficient needs further investigation. With regard to the relationship of fat and protein in the food to the ammonia coefficient of infants not severely ill, it can be said that, within certain limits, and for a given individual, high protein tends to lower the ammonia coefficient, and low protein, to increase it. This is mainly brought about by an increase in total nitrogen excretion on a high protein diet, while the total ammonia excretion may be influenced to a lesser extent. An increase of fat in the diet tends to increase the ammonia coefficient. It follows that within certain limits the ammonia excretion is influenced by the ratio obtaining between the fat and protein of the food.

It is not uncommon for the diaper of infants to have an ammoniacal odor. The urine as voided does not contain free ammonia; this is readily formed from urea by the action of a special microorganism (mikrococcus ureae, Cohn), or rather by the bacillus ammoniagenes, Cooke. As a rule, boiling of the diapers and final rinsing out of 1:5000 bichlorid of mercury prevents this formation of ammonia.*[93, 182]

* The retention of alkali in a diaper washed with a strongly alkaline soap and not sufficiently rinsed has also been made responsible for the liberation of ammonia.[411]

The liberation of ammonia from its salts may also have to be taken into consideration under certain conditions.

The excretion of ammonia may be decreased very markedly by the administration of alkali.

In certain cases, such as severe gastro-enteric disorders, diabetes, or fasting, the ammonia excretion may be much increased. The ammonia coefficient in cases of gastro-intestinal disturbances may rise to about 50 per cent. Czerny and Keller regard a definite increase in the total ammonia excretion accompanying an increased ammonia coefficient as the result of an acidosis. This is not generally accepted. Whether an increase of the ammonia coefficient alone may serve as an indication of an acidosis (absolute or relative, that is, alkalipenia) is very doubtful.

Uric Acid.—The uric acid excretion is of special interest during the first few days of life, a period during which uric acid infarct occurs regularly. It shows itself in the urine by the presence of hyaline or granular casts or spheres incrusted with uric acid or its salts. These elements are identical with those found in the kidney infarcts. The infarct period is chiefly confined to the second half of the first and the second day after birth. The exciting cause is seen by Flensburg in the excretion of an albuminous material into the convoluted tubules during fetal life and shortly after birth. This material forms the casts on which ammonium urate is deposited. During the first few days, particularly the second and third, Sjöquist found a rather high uric acid excretion. These findings found corroboration by Reusing and by Schloss and Crawford. Calculated from the results of the latter authors, with correction for time, the excretion of uric acid averaged 70 mg. during a period comprising the first three days; it dropped during the next three days, to about 50 mg., and then to 37 mg. Late ligation of the cord makes the excretion of the first period somewhat higher. The excretion of uric acid may be associated with a relatively high phosphoric acid excretion. Both may perhaps be related to a relatively high number of leukocytes in the blood, a breakdown of a large number of these being supposed to furnish the nucleic acid from which uric and phosphoric acid are derived.*

The excretion of uric acid in the urine of infants raised on breast and cow's milk, differs from that of the total nitrogen and urea in that it is independent of the amount of food. Colostrum, as well as human and cow's milk, are not entirely free from purin bodies; [86,333,395] nevertheless the amounts introduced in this manner, together with the apparently relatively poor absorption of orally introduced purines justify the assertion that the greatest part of the uric acid of the infant is of endogenous origin.

This does not exclude all influence of the diet on its excretion. The investigations of Orgler[282] indicates that the addition of carbohydrates to the food may be followed, under certain conditions, by a

* It is of interest that Sedgwick and Kingsbury report a rather high uric acid content of the blood during early life.

decrease in the uric acid excretion. This influence can only be brought about indirectly. By their influence on nitrogen retention, the carbohydrates may create conditions more favorable to the synthesis of nucleoproteid. The observations of Orgler were made on infants, either with a slight gastro-intestinal disturbance, or in a period of recovery therefrom.

Table 14.—Approximate Averages for Endogenous Uric Acid (Kern)

Age	Weight, kilogram	Uric acid	
		Milligram	Milligram for each kilogram
2.5 months	4.2	45	10.7
4.5 months	5.0	52	10.4
4.5 months	5.4	60	11.1
6.5 months	4.5	44	9.8
4.0 months	5.3	55	10.4
3.5 years	15.0	150	10.0
7.0 years	24.0	100	4.2
8.0 years	18.5	90	4.8
11 years	27.0	180	5.5
12 years	35.5	170	4.7
Adult 35 years	65.0	100 to 200	1.5 to 3.0

The absolute amount of uric acid increases with advancing weight and age, while the relative amount, that is, the amount excreted for each kilogram of body-weight decreases. Gundobin's data tabulated by Mayerhofer[244] show an increase of the absolute, as well as of the relative amount with advancing age. But these data cannot represent the endogenous uric acid excretion. For instance, for the ages from nine to 10 years the total excretion is given as 0.5682 gm. and from 11 to 12 years as 0.7065 gm. with 20 mg. and 23.4 mg. for each kilogram. In the adult the endogenous uric acid excretion does not often exceed 0.5 gm. The figures given by Kern may be exceeded. Utheim reports the cases of four normal babies fed on whole milk mixtures, in whom the uric acid excretion varied from about 81 to 240 mg. with about 11 to 33 mg. for each kilogram of body-weight. In a number of sick infants, the greater number of which were in a state of athrepsia, the uric acid output was not strikingly different, except in one instance, in which a three and one-half month infant with acute diarrhea was fed protein milk, and a total of 410 mg. uric acid was excreted, with 78 mg. for each kilogram of body-weight (Table 15).

The weight of these children reported by Johnson and Veeder is not given. They were on a diet free from creatinin, which happens to be also a so-called purin-free diet. The first and third had a negative

nitrogen balance, without taking into consideration the loss of nitrogen in the stools.

TABLE 15.—ABSOLUTE AMOUNTS OF URIC ACID EACH DAY (JOHNSTON AND VEEDER)

Age	Uric acid, milligrams
29 months	264
36 months	261
6 years	276
8 years	324
8 years	327
9 years	240
10 years	549
14 years	264

The excretion of endogenous uric acid may be fairly constant from day to day in the same person, but considerable variations may occur.

The participation of the uric acid nitrogen in the total nitrogen is not great. The variations are chiefly dependent on variations in the output of total nitrogen. Folin[105] awards 1.1 per cent. of the total nitrogen to uric acid on a diet rich in protein, and 2.5 per cent. on a diet poor in protein. At the same time the total uric acid decreases. In the cases of Schloss and Crawford, about 11.2 per cent. of the total nitrogen fell to the share of uric acid during the period comprising the first three days of life; during the second period it was about 5.5 per cent. and during the third 4 per cent. These newborn infants were breast fed. In the cases of Orgler, the infants from one to one and one-half months of age, fed on human milk, registered 5.2, 5.9, 6 and 2.9 per cent. The conditions were not ideal. On artificial feeding the total uric acid excretion was greater than on human milk. However, these results will not be discussed here. It is very doubtful whether infants doing well on artificial food and infants doing well on the breast will show any marked differences in uric acid excretion.

In the breast fed infant one month old, observed by Amberg and Morrill,[16] the uric acid nitrogen constituted 3 per cent. of the total nitrogen. On a diet a little above maintenance, and low in protein, the total uric acid excretion was a little higher, and the uric acid nitrogen percentage rose to more than double. The cases of Johnston and Veeder in which the children were not all on a purin-free diet, the excretion of uric acid nitrogen was from 0.8 to 2.9 per cent. These children, 21 in number, varied in age from 19 months to 14 years. In certain cases of infantilism Herter described increased uric acid excretion varying from 380 to 545 mg.

Since uric acid is derived from nucleic acid, the prosthetic group of the nucleoproteids, it is to be expected that any diseases accompanied by a disintegration of cell nuclei may be associated with an increased uric acid excretion. Increased uric acid excretion has been found in

fevers, at the time of resolution of a pneumonia, leukemia, extensive burns, and exposure to roentgen rays, and so forth. That a leukocytosis alone need not necessarily lead to an increase of uric acid excretion is shown in the results of Bruck and Wedell in cases of whooping cough. The number of leukocytes in these cases did not exceed 35,000.

When food containing nucleic acid is added to the diet, the uric acid of the urine increases, and this increase is dependent on the amount of certain purins in the food. The uric acid derived from the food is called exogenous uric acid. The addition of sweetbreads or of sodium nucleinate to a purin-free diet given to a normal individual leads to a rapid increase of the uric acid and a rapid return to normal, within little more than one day. In certain pathologic conditions, particularly in gout, the uric acid excretion does not rise as rapidly, and the return to normal is delayed. Such a delay was observed by Kern in cases of exudative diathesis on the administration of sodium nucleinate. In some of his cases this delay was very definite, in others less so. Uffenheimer[384] describes delayed uric acid excretion after the addition of calf's sweetbread to the diet in one case of bronchial asthma, one case of neuropathy and in one case of eczema with pseudoscrofulosis and lymphatism.

Uric acid is of further clinical interest on account of stone formation. Investigations like those of Orgler,[282] Niemann,[275] Birk,[49] and Schloss and Crawford show that uric acid need not be the only representative of the nucleic acid metabolism in the urine. The infant may excrete daily from a trace to about 15 mg. or more in a form usually designated as "other purin bases." In one case Niemann found on the third day after birth the extraordinary amount of about 53 mg. The data are somewhat unreliable, owing to the methods by which the results were obtained.

Wiechowski notes that Baginsky found 25.8 mg. xanthin in 100 c.c. urine from nephritic children, while normal children excrete only 3.8 mg. xanthin in 100 c.c. The purin bases, other than uric acid, which enter into consideration chiefly as possible constituents of urine, are adenin, guanin, xanthin and hypoxanthin. At one time it was claimed that the infant's urine contained allantoin, an oxidation product of uric acid. This claim could not be substantiated.

It must not be forgotten that neither phosphoric acid nor purine excretion can give a comprehensive picture of the nucleic acid metabolism. The fate of the sugar contained in its molecule has not been touched on for want of data. Under usual conditions it seems that the nitrogen of the pyrimidin fraction, containing thymin and cytosin in animal nucleic acids, appears in the urine in the form of urea, but whether this always happens when larger amounts of nucleic acid undergo decomposition is not certain.

Creatin and Creatinin.—Chemically creatinin and creatin are closely related, creatinin being the anhydrid of creatin. A number of investigations indicate that both substances are mainly connected with muscle metabolism.[257,355,366]

In the experiments of Benedict and Osterberg,[40] extending over a prolonged period of time, creatin administered to the dog by mouth was partly excreted as such. Almost with the cessation of administration, the creatinuria ceases. But of the retained creatin, about 30 per cent. was finally excreted in the form of creatinin. The close relationship between creatin and creatinin would suggest a priori a definite relationship in their metabolism and in their secretion, so that their sum would be of special significance. This has been claimed by Harding and Gaebler for the period of growth in which creatin forms a regular constituent of the urine. Three groups of children were examined, each composed of two boys and two girls. In the first group with an age of two and one-half to three and one-half years, the diet contained about 5 gm. protein for each kilogram of body weight; in the second, four to four and one-half years of age, about 4 gm. for each kilogram, and in the third, in which the age was nine to nine and one-half years, about 3 gm. for each kilogram. The creatinin plus the creatin is given in terms of creatin, and the excretion of total creatin for each kilogram of body weight, their "total creatine coefficient" was found to be constant. It averaged for the first group 23.2, for the second 22.1 and for the third 23.9. The variations within the groups were rather insignificant. But it remains to be seen whether this constancy will prevail with a larger number of observations throughout infancy and childhood, under similar conditions. The relationship of one to the other in the economy of the organism is not clear. Contrary to former views, it seems that creatin administered to animals and man can lead to an increase of creatinin excretion in the urine[222,251,304]. Its amount is dependent in part on the amount present in food, particularly in meat. Another part is of endogenous origin, and this part is rather constant for the normal person, although subject to somewhat wider variations than was at first believed. Even the excretion hour by hour may be very uniform. Folin established a certain relationship between the creatinine excretion and the body weight. His observations that fat persons excreted relatively less creatinin than lean persons, led to the conclusion that the chief factor determining its elimination was the active mass of protoplasm. Later Shaffer and others regarded the creatinin excretion as chiefly dependent on muscle metabolism. This would mean an interrelation between muscle mass and creatinin excretion. As far as the body weight indicates muscle mass (or active protoplasm), the calculation of the creatinin for each kilogram of body weight is of special significance.

In spite of the correlation between creatin and creatinin their excretion must be discussed separately, because, among other reasons, creatin excretion may vary from that of creatinin. Creatinin is excreted in urine throughout life. If administered, the greater part appears in the urine as such.

Shaffer,[354] with the utilization of the results of Folin and others, gives data according to which the normal adult male excretes from 0.8 to 2.2 gm. endogenous creatinin in the course of twenty-four hours, or

about 15 to 30 mg. for each kilogram each day. This is called by certain authors the creatinine coefficient; others use the term as does Shaffer, to denote the amount of creatinine nitrogen in milligrams for each kilogram of body weight and each day. The range of this coefficient would be about 5.5 to 11.7. Active persons, who are not too fat, excrete rarely less than 18 mg. creatinin for each kilogram, the creatinin coefficient of Shaffer being rarely less than 7. Benedict and Myers and Krause and others ascribe to women a creatinine excretion of about 7 to 22 mg. for each kilogram, while McLaughlin and Blunt insist that the creatinine coefficient of normal women falls well within the normal limit defined by Shaffer for the male.

Tables 16 and 17 contain data for the normal creatinine excretion in infancy and childhood. For convenience, the data of creatin are also given. Table 16 gives the total 24 hour excretion in milligrams during the first week of life. The daily variations in the same infant are marked. Sedgwick[348] justly remarks that the retention of a few cubic centimeters of urine in the bladder at the end of a 24 hour period would cause considerable differences in the results in cases in which the daily quantity of urine is so small. Partly for this reason the values are not quite correct. The number of available observations is also rather small.

TABLE 16.—CREATININ AND CREATIN IN MILLIGRAMS EACH DAY

Author		Day of life							
		1	1 and 2	2	3	4	5	6	7
Amberg and Rowntree	1	.....	20.7						
	2	.....	5.7						
	3	.....	6.5						
	4	.....	17.4						
	5	.....	8.5						
Sedgwick[347]	1	.....	.....	24.9	11.7	25.8			
	2	4.5	.....	19.8	4.0	6.7	11.9	18.0	
	3	11.8	.....	.....	50.5	17.4	28.2	32.6	16.0
Creatin	...	.....	.....	0	.....	4.27	2.12	10.1	
	4	.....	.....	33.0	10.0	21.0	12.1	30.3	
Creatin	...	.....	.....	0.5	.....	1.76	6.86		
	5	13.2	.....	10.1	.....	4.0	12.4		
Creatin	...	.....	.....	.....	.....	.....	5.39	7.83	
	6	.....	.....	31.6	.....	20.0			
Creatin	...	.....	.....	3.82					
	7	25.5	.....	14.1	10.7	.....	25.3	14.9	
Simon[359]	1	.....	.....	1.4	8.1	10.8	13.5	13.5	13.5
	2	.....	.....	.....	.....	.....	.....	8.1	10.8
	3	.....	.....	.....	.....	.....	8.1	5.4	
	4	.....	.....	.....	.....	.....	8.1	8.1	

Table 17 includes observations on infants and children beyond the first week of life on so-called creatinine and creatin-free diets. With the exception of the case of Schwartz, milk, which is not entirely free from creatinin and creatin, formed part of the diet. Denis and Minot found from 1.0 to 1.5 mg. creatinin and 2.0 to 2.6 mg. creatin for each 100 c.c. of cow's milk. Human milk contains 1.0 to 1.5 mg. creatinin and 1.9 to 3.9 mg. creatin.[86] In infants and children on diets containing milk and even some meat, the creatinin nitrogen participates in the total urinary nitrogen with about 1 to 3 per cent. In the adult, Folin showed (Table 17) that creatinin nitrogen formed 3.6 per cent. of the total nitrogen on a diet rich in protein, while on a diet poor in protein with lessened total nitrogen excretion it rose to 17.2 per cent. This may be mainly owing to the fact that the creatinin excretion is in a large measure independent of the protein intake. The total creatinin output in the child is lower than in the adult, as is to be expected. The excretion for each kilogram of body-weight also falls below that of the adult. There is a gradual rise of the creatinin output, so that from about the tenth year, the output for each kilogram approaches rapidly that of the adult. Ederer gives for children of from two to six years, about 7.0 to 17 mg. creatinin for each kilogram of body-weight, and for those of from seven to ten years, about 15 to 21 mg. The figures of Harding and Gaebler average 12 mg. for children of from two and one-half to three and one-half years; 14 mg. for those of four to four and one-half years, and 18 mg for those of nine to nine and one-half years. During fasting the creatinin excretion in the adult shows more or less decrease; in infants and children, the data are insufficient. In the case of Amberg and Morrill, there was an increase. In the cases of Gamble, Ross and Tisdall a gradual decrease occurred in one child who fasted 15 days; one fasting 10 days showed an irregular slight decrease, and one fasting four days showed a slight increase in the total creatinin output. In a two months old infant with pyloric stenosis, Cutter and Morse found at a time when the weight was dropping rapidly, that the creatinin output was 144 mg. in 24 hours; a little over a month later, when the infant was doing well, the creatinin output was 295 mg. So far as can be estimated from their data the excretion for each kilogram of body-weight rose from about 5.5 to 8 mg. This result would indicate the possibility of a diminished creatinin excretion of the infant in the course of prolonged marked undernutrition. The same authors report a very marked, though temporary, reduction of the creatinin excretion in two cases of nephritis, which may mean a retention. In the case of infants with nutritional disorders Utheim found the amount of creatinin somewhat lower than in the norm. Certain observations of Ederer also point in this direction.

Special interest is attached to cases in which the muscular system is especially affected. Thus Spriggs found a daily output of 62.5 mg. creatinin, and 4 mg. for each kilogram in a boy four and one-half years of age, suffering with amyotonia congenita. Gittings and Pemberton

found that a 21 months old infant excreted daily 16.6, or 1.7 mg. for each kilogram of body-weight. Spriggs and others report a relatively low creatinin excretion in two cases of muscular dystrophy, and Greenwald, for a female cretin seven years of age, reports 45 to 58 mg., or 3.1 mg. for each kilogram. Utheim, on the contrary, found an increase of creatinin in a six months' old cretin (29.3 to 56 mg. each day, 9 to 19 mg. for each kilogram). While certain other conditions in the adult, for instance, exophthalmic goiter, have been associated with a diminished output of creatinin, there has been an increased output in fevers. A number of determinations of creatinin have been reported in a variety of disorders, but it is impossible to connect definite changes in creatinin excretion with any of these.*

Creatin has been found and is accepted as a normal constituent of the urine of infants and children, and occasionally of women. The normal adult male does not excrete creatin on a creatin-free diet.†

Creatin appears in the urine of adult man under various pathologic conditions associated with more or less cachexia, such as malignant tumors, diabetes, hyperthyroidism and acute fevers. Bürger[62] found it in a case of trichinosis. This author gives a good review of the diseases associated with changes in the creatinine and creatine output.[63]

Some of the available data concerning the creatine excretion in infants and children are found in Table 17. Only the total 24-hour excretion is registered. The table does not include the results of Rose,[311] who found creatin in boys and girls up to 15 years of age. He gives figures for the creatine excretion for each 100 c.c. of urine, and had no control of the diet. In only one of nine boys 10 to 15 years of age was creatin absent, and in only one of eight girls of the same age. Krause has not found creatin in the urine of boys from the seventh year. Folin and Denis[106] found creatin in the urine of two boys, one eight years old, the other 17. The latter was raised a vegetarian. It seems that creatin need not always occur in older boys. The same may be said of women; not all women need excrete creatin, or at least not regularly. In any event the absence of creatin from the urine of normal children, up to the age of five years, is decidedly rare. In the infant, with pyloric stenosis already mentioned, during a period of falling weight and shortly after the turn of the weight curve upward, no creatin was found; it appeared later. In cases of myxedema in childhood, the creatin may be absent or much diminished, but it appears on thyroid medication In creatinism, the

* Observations on a number of infants have been reported by Schiff and Bálint, and creatin determinations are included (Table 18). The figures representing creatinin excretion are on the whole much higher than those of others for infants of the same age. For this reason the figures are given separately. However, more severe disorders of nutrition also are accompanied by a relatively low creatinin output.

† "On a number of different occasions the urine of normal men on a creatinine- and creatine-free diet was found to contain small quantities of creatin. So far, it has been impossible to determine under what conditions this may occur."[197]

TABLE 17.—CREATININ AND CREATIN EXCRETION IN INFANTS AND CHILDREN BEYOND THE FIRST WEEK OF LIFE

Author	Sex	Age				Weight, kilograms	Creatinin, milligrams each day	Creatin, milligrams each day	Creatinin, milligrams for each kilogram each day	Protein, grams each day	P_H	Remarks
		Days	Weeks	Months	Years							
Amberg and Morrill	M	7	..	....	.....	3.0	17.5	.....	5.5			
	M	10	..	....	.....	4.0	26.8	.....	2.5			
	M	10	..	....	.....	3.5	26.9	.....	2.9			
	M	13	..	....	.....	3.0	30.1	2.9	3.6			
	M	14	..	....	.....	2.7	27.1	.....	3.7			
	M	..	..	1.0	.....	4.7	38.5	5.8	8.2	12.8		
	....	..	..	....	.....	....	29.62	8.6	6.3	11.4		
	....	..	..	....	.....	....	37.6	5.6	8.0	10.8		
	....	..	..	....	.....	4.5	48.2	0.5	10.7	....	...	Water diet (last 48 from 66 hours fasting)
	....	..	..	....	.....	....	33.2	6.5	7.4	4.1		
	....	..	..	4.6	.....	4.6	29.9	4.1	6.5	3.5		
	....	..	..	....	.....	....	31.4	5.9	6.8	3.2		
Funaro	....	..	..	1.5	.....	3.5	17.5	.....	5.0			
	....	..	..	2.0	.....	4.0	21.0	.....	5.3			
	....	..	..	2.5	.....	4.3	28.0	.....	6.5			
	....	..	..	3.0	.....	4.4	31.2	.....	7.1			
	....	..	..	3.0	.....	4.0	30.4	.....	7.6			
	....	..	..	3.0	.....	4.8	42.0	.....	8.8			
Ederer	....	..	7	....	.....	4.8	39.1	.....	8.1	....	...	Breast milk
	....	..	..	....	.....	....	47.6	.....	9.9			
	....	..	10	....	.....	5.2	58.5	.....	11.4	....	...	Breast milk
Sedgwick	M	..	..	6.0	.....	5.6	76.1	.....	13.6			
Talbot and Gamble	M	..	..	5.25	.....	4.3	62.1	9.3	14.4	10.2	5.8	
	....	..	..	5.75	.....	4.4	54.0	37.2	12.3	20.0	6.1	
	....	..	..	6.0	.....	4.7	59.4	80.6	12.6	23.3	6.5	
	....	..	..	6.5	.....	4.9	56.7	77.5	11.8	29.5		
	....	..	..	6.75	.....	5.1	62.1	120.0	12.2	36.2		
Gamble and Goldschmidt	M	..	..	10.0	.....	6.5	78.0	68.0	12.0	20.0	6.4	
	....	..	..	to	.....	to	82.0	116.0	11.7	30.0	6.3	
	....	..	..	12.0	.....	7.1	63.0	54.5	9.0	12.0	6.4	
	M	..	..	14.0	.....	6.5	70.0	71.9	10.8	....	6.2	

TABLE 17.—CREATININ AND CREATIN EXCRETION IN INFANTS AND CHILDREN BEYOND THE FIRST WEEK OF LIFE.—(*Continued*)

Author	Sex	Age				Weight, kilograms	Creatinin, milligrams each day	Creatin, milligrams each day	Creatinin, milligrams for each kilogram each day	Protein, grams each day	P_H	Remarks
		Days	Weeks	Months	Years							
Denis and Kramer	M	..	..	13.0	.....	9.6	100.0	102.0	10.4	53.0		
	....	..	..	....	.....	....	99.0	56.0	10.3	7.8		
	....	..	..	....	.....	....	110.0	81.0	11.5	7.8		
	....	..	..	....	.....	....	99.0	53.0	10.3	7.8		
Gittings and Pemberton	....	..	..	....	2.75	11.0	78.6	.....	7.0			
	....	..	..	....	3.33	11.0	89.0	.....	8.0			
Schwartz[346]	M	..	..	....	5.0	23.5	404.0 to 454.0	.....	16.5 to 20.8	....	...	Seven-day period, no milk
Folin and Denis[106]	F	..	..	....	3.75	16.0	190.0	90.0	11.9			
	M	..	..	....	8.75	33.5	620.0	100.0	18.5			
	....	..	..	....	.....	....	385.0	119.0	11.5			
	....	..	..	....	.....	....	481.0	150.0	14.4			
	F	..	..	....	11.0	38.0	720.0	160.0	19.0			
	....	..	..	....	.....	....	399.0	140.0	10.5			
	....	..	..	....	.....	....	477.0	86.0	12.5			
Krause	M	..	..	....	7.0	30.0	243.0	140.0	8.1	....	...	Convalescent
	M	..	..	....	11.0	28.4	305.0	34.1	10.7	....	...	Slight idiosyncrasy
Sawyer, Stevens and Baumann.	M	..	..	....	5.0	23.0	276.0	192.0	12.0	....	...	Only the first control days are taken from the tables
	....	..	..	....	.....	....	274.0	194.0	11.9			
	....	..	..	....	.....	....	274.0	174.0	11.9			
	M	..	..	....	6.0	18.3	281.0	72.0	15.4			
	....	..	..	....	.....	....	264.0	61.0	14.4			
	M	..	..	....	5.0	20.5	336.0	184.0	16.4	....	...	Large tonsils and mental deficiency
	....	..	..	....	.....	....	332.0	141.0	16.2			
	M	..	..	....	8.0	23.2	332.0	96.0	14.3			
	....	..	..	....	.....	....	362.0	86.0	15.6			
	....	..	..	....	.....	....	336.0	143.0	14.5			

Krause	F	..	..	....	5.0	....	186.0	16.0				
	....	..	..	....	.....	....	230.0	28.0				
	F	..	..	....	6.0	....	86.0	9.3				
	....	..	..	....	.....	....	167.0	36.3				
	....	..	..	....	.....	....	213.0	12.4				
	F	..	..	....	10.0	....	397.0	60.0				
	....	..	..	....	.....	....	437.0	45.0				
	F	..	..	....	11.0	....	203.0	0.0				
	....	..	..	....	.....	....	332.0	0.0				
	F	..	..	....	12.0	....	543.0	33.0				
	....	..	..	....	.....	....	513.0	trace				
	....	..	..	....	.....	....	605.0	126.0				
	....	..	..	....	.....	....	562.0	30.0				
	M	..	..	....	2.0	....	68.0	39.0				
	....	..	..	....	.....	....	68.0	36.0				
	M	..	..	....	3.0	....	68.0	27.0				
	....	..	..	....	.....	....	78.0	27.0				
	....	..	..	....	.....	....	65.0	74.0				
	M	..	..	....	5.0	....	302.0	78.0				
	....	..	..	....	.....	....	335.0	87.0				
	....	..	..	....	.....	....	273.0	65.0				
	M	..	..	....	7.0	....	130.0	40.0	....	....	...	Convalescent
	....	..	..	....	.....	....	367.0					
	....	..	..	....	.....	....	507.0					
	M	..	..	....	8.0	....	471.0					
	....	..	..	....	.....	....	440.0					
	M	..	..	....	10.0	....	343.0	.....	....	....	...	Convalescent
	....	..	..	....	.....	....	454.0					
	....	..	..	....	.....	....	408.0					
	....	..	..	....	.....	....	364.0					
	....	..	..	....	.....	....	364.0					
	M	..	..	....	12.0	....	232.0					
	....	..	..	....	.....	....	424.0					
	....	..	..	....	.....	....	408.0					
	M	..	..	....	13.0	....	664.0					
	....	..	..	....	.....	....	724.0					
	M	..	..	....	15.0	....	1020.0					
	M	..	..	....	16.0	....	724.0					
	....	..	..	....	.....	....	1010.0					
Harding and Gaebler	Girls	..	..	....	2.5 to 3.5	....	173.0	138.0	....	....	...	Daily averages of three-day periods.
	....	..	..	....	.....	....	141.0	145.0				2.5 to 3.5 years about 5 gm protein for each kg.
	....	..	..	....	4.0 to 4.5	....	223.0	100.0				4.0 to 4.5 years about 4 gm. protein for each kilogram.
	....	..	..	....	.....	....	276.0	109.0				9 to 9.5 years about 3 gm. protein for each kilogram.
	....	..	..	....	9.0 to 9.5	....	524.0	187.0				
	....	..	..	....	.....	....	439.0	259.0				
	Boys	..	..	....	2.5 to 3.5	....	180.0	121.0				
	....	..	..	....	.....	....	200.0	125.0				
	....	..	..	....	4.0 to 4.5	....	281.0	90.0				
	....	..	..	....	.....	....	261.0	77.0				
	....	..	..	....	9.0 to 9.5	....	454.0	90.0				
	....	..	..	....	.....	....	476.0	36.0				

TABLE 18.—CREATININ DETERMINATIONS (SCHIFF AND BÁLINT)

Age, months	Weight, kilogram	Creatinin, milligram each day	Creatin, milligram each day	Creatinin, milligram for each kilogram each day	Diet
7	4.2	109.3	10.0	26.0	Butter-flour mixture
5	4.3	118.8	14.4	27.6	Butter-flour mixture
2.5	3.9	69.0	11.5	17.7	One-half milk mixture
5	5.2	127.6	31.1	24.5	Light chronic disorders
4	3.5	84.0	33.6	24.0	of nutrition
4.5	4.1	112.0	28.0	27.3	
6	4.7	65.7	18.8	14.0	Severe chronic disorders
6	4.0	68.5	24.5	17.0	of nutrition
6	4.0	70.2	30.5	17.6	
3	3.2	42.8	3.8	13.4	Severe inanition
	3.5	92.3	14.2	26.3	Improving

creatin output may also be low.[173] During starvation, creatin appears in the urine of adult males; in women, if present before starvation, it increases. Sufficient data with regard to infants and children are not available. In the case of Amberg and Morrill creatin practically disappeared on a water diet. In certain observations on animals, the creatin first diminished on fasting. In conditions associated with acidosis, the creatin excretion rises, as in the cases of Sawyer, Stevens and Baumann, in which acidosis was produced by dietary measures.* In the case of a boy, aged six years, reported by Mellanby, in an attack of recurrent vomiting, the creatin rose to 0.7 gm. in such conditions several factors, such as fever, inanition and acidosis, may enter into consideration. But while acidosis is associated with creatinuria, this cannot be suppressed entirely by the administration of alkali. Neither is the absence of carbohydrates from the food the all-important factor, as has been claimed, even if the creatinuria of starvation may be overcome by carbohydrates. The administration of alkali to fasting animals diminishes the creatinuria, or may even suppress minor degrees of it; the same is true for carbohydrates. But the administration of starch and alkali to a fasting pig to the extent that the urine became alkalin had a doubtful effect on the creatine excretion.[373] Underhill and Bogert assert that creatine elimination in the urine may be induced by at least two different sets of conditions, (1) creatin may appear in the urine in states of acidosis in which carbohydrate deficiency is not involved, and (2) creatinuria may be present during carbohydrate deficiency even in the absence of acidosis. While in starving animals protein feeding may inhibit the creatinuria,[370] high protein feeding in infants and children, as well as in adults, with hyperthyroidism, either induces creatinuria, if not already present, or if present, increases it.[84, 85, 121, 378] Rose, Dimmitt and Bartlett deny emphatically an influence of protein feeding on the provocation or increase of creatin-

* Anoxemia in animals, of several days' duration, leads to a marked increase of the creatine output.[341]

uria. From the experiments of Gamble and Goldschmidt it appears that the creatine content of milk is not a negligible factor in such experiments, particularly if it is remembered that administered creatin is perhaps more readily excreted by children than by adults, and by adults more readily on a high than on a low protein diet. It is to be expected that smaller amounts of creatin lead to an excretion of creatin in the child's urine than in the adult's, and this has been demonstrated by Beumer[44] for infants and children on oral as well as intravenous administration.

The most unfavorable condition for the excretion of creatin in the urine seems to be a low protein diet. There is one very important exception to the rule that creatinuria may be caused by high protein feeding; thus far high protein feeding has not produced creatinuria in the adult male. Denis and Minot fed protein to the extent that 34.5 gm. nitrogen were excreted in the urine without the appearance of creatinuria.

If it is true that creatin disappears in boys approaching, or at the time of puberty, and does not occur in the normal adult male, while it does occur in women even if irregularly,[310] another factor for its excretion or perhaps better for the prevention of its excretion obtrudes itself: the possible influence of the human male sexual glands. Thus Read found persistence of creatinuria in Chinese eunuchs, and McNeal was able to demonstrate the presence of creatin in the adult male when destruction of the testicles had occurred, or when impotence or a probably organic basis had supervened.

Hippuric Acid.—Hippuric acid is normally encountered in the urine of the adult. As early as 1866 Meissner and Shepard said that its occurrence in infant's urine is well known. Simon[359] found in two cases a total 24 hours excretion of 45 to 83 mg. for the first eight days of life. The nitrogen formed 0.7 to 2.2 per cent. of the total. For the period of the first three days the excretions were higher. The age of the infants in the cases of Amberg and Helmholz[11] varied from two to fourteen months. Most of the cases were not normal. The excretion varied between 14 and 70 mg. in 24 hours,the hippuric acid nitrogen being less than 1 per cent. of the total. Amberg and Helmholz used a different method from that employed by Simon.[359] The ability of the kidney to synthetize hippuric acid from benzoic acid and glycocoll is of especial interest.

Amino Acids and Rest Nitrogen.—The methods for the determination of the oxyproteic acids stand in need of improvement.[322] Simon[359] used the method of Ginsberg who ascribed 3.1 to 5 per cent. of the total urinary nitrogen of the adult to these acids. During the first week of life Simon determined 2.6 to 9.8 per cent. of the total nitrogen belonging to the oxyproteic acids; later in infancy 4.7 to 11.7 per cent. Utheim says that the oxyproteic acid nitrogen may be as high as 10 per cent. of the total nitrogen in athreptic infants, with an average of about 5 per cent., while normal infants excrete about 1 to 1.5 per cent. of the total nitrogen in this form. The existence of

an oxyproteic acid as a sulphur-containing entity, has recently been denied by Freund and Sittenberger-Kraft.

For the polypeptids Simon* gives certain data for the first eight days of life. The nitrogen was from 38 to 100 mg., being about 13 to 20 per cent. of the total. In the three cases of Goebel[130] in which the polypeptid nitrogen was determined separately, it amounted to about 1.2 to 1.6 per cent. of the total nitrogen. The infants were from six to 45 days of age.

The Henriques-Sörenson method ascribes about 1 to 2 per cent. of the total nitrogen to the amino-acid fraction of the normal adult's urine. The number of observations in infants and children is not great. Observations on normal infants are particularly scarce. Simon,[359] with a method giving too high values during the first week of life, found 13 to 30 mg. nitrogen excreted in the amino-acid fraction, forming about 4 to 14 per cent. of the total nitrogen. From then to about the third month, the excretion was 16 to 91 mg. nitrogen, or about 8 to 14 per cent. The data given by Simon and by Schlutz for infants from two and one-half to 16½ months of age, nearly all subject to more or less severe nutritional disorders, varied from 20 to 284 mg., about 2 to 17 per cent. of the total nitrogen. The results of Hadlich and Grosser are calculated for each 100 c.c. of urine. The normal breast-fed infants, four to six months of age, including an infant observed by Simon, excreted 1.5 to 5 per cent. of the total nitrogen in the amino-acid fraction, artificially fed infants with various ailments about 1 to 4 per cent., infants with slight disorders of nutrition, 2 to 8 per cent., and those with severe nutritional disorders 1.5 to 14 per cent. A child of two years, with severe enteritis, excreted 28.5 per cent. of its nitrogen in this fraction; older children with various ailments excreted about 1 to 5 per cent. In Krause's cases the children from 5 to 11 years of age excreted from 35 to 91 mg. of amino-acid nitrogen forming 1 to 2 per cent. of the total nitrogen.

The results of Goebel (formol titration) were obtained in infants from six days to 14 months of age. Here also the amino-acids are recorded for each 100 c.c. urine. The nitrogen of the amino-acids formed about 1.4 to 8.9 per cent. of the total urinary nitrogen. Thirteen of the 24 infants were not normal. Of the 26 determinations, five fell below 3 per cent., and only one of these within the first three months. Of seven determinations in children from six to 10 years of age, the amino-acid nitrogen was about 1.4 to 2.8 per cent. of the total, which compares well with the percentages of the adult. In three infants with alimentary intoxication, no unusually high values were obtained. In a number of premature infants, it was found that in the

* In the two cases in which the polypeptids were determined, urea and ammonia nitrogen were determined, and the remainder is given as total rest nitrogen. This total rest nitrogen is made up of the nitrogen of amino-acids, hippuric acid, polypeptids, oxyproteic acids, each of which was determined separately. Besides, there is a column giving non-determined rest nitrogen. The sum of these various fractions exceeds the total rest nitrogen considerably.

first days after birth the nitrogen fraction of the amino-acid did not differ from that of infants generally, but rose from about the end of the second week to percentages of about 10 to 25. This increase was observed during about the first half year of life. The total amount of amino-acid nitrogen for each 100 c.c. urine did not, as a rule, show a corresponding increase. As with other nitrogenous substances, the percentage of nitrogen excreted in the form of amino-acid is frequently dependent on the total nitrogen excretion. Goebel[131] with Ylppö[410] classifies as premature, infants whose birth weight is less than 2500 gm. Short fasting seems to lead to a decrease of the amino-acid nitrogen percentage. Protracted fasting (72 hours) in the newborn led to an increase of the percentage (25 per cent). Intravenous injection of glycocoll raised the percentage still further, to about 37 per cent. In an infant two weeks old, Utheim, who also records the excretion of amino-acids for each 100 c.c. of urine, 9.7 per cent. of the total nitrogen was excreted in the form of amino acids, (method of Van Slyke). The normal infant, four weeks to eighteen months of age, excreted 0.3 to 4.1 per cent. of their urinary nitrogen in this form. In certain cases of ileocolitis and athrepsia the latter percentage was appreciably surpassed, the highest being 12 per cent. Values higher than 5 per cent. were obtained in 16 of 58 determinations. Among this number fall six of 11 cases of athrepsia.

Meyer and Rietschel,[253] and Simon and Schlutz fed infants glycocoll or alanin. Only in severe cases of intoxication or of nutritional disorders did some of the introduced amino-acid appear in the urine. Neither could Goebel recover any glycocoll, inactive leucin, or tyrosin administered in single doses of 2 to 3 gm. Samuely and von Reuss claim the occurrence of free glycocoll in the normal infant's urine. Goebel found it only once in the urine of a premature infant. In cases of acute yellow atrophy of the liver, leucin and tyrosin have been found in the urine.

In most studies of nitrogen partition in the urine, the so-called rest nitrogen is discussed. This represents the difference between the total nitrogen and the sum of nitrogen in the various nitrogenous constituents which have been quantitated. It is evident that the percentage of this rest nitrogen is subject to rather wide variations. In the majority of cases it includes nitrogen derived from amino acids, oxyproteic acids, polypeptids and the products of the nucleic acid metabolism other than uric acid. Furthermore, indoxyl derivatives, amines, guanidins, and so forth may be represented.

Indican.—Indican, the mother substance responsible for the indigo blue reaction of the urine, is regarded as the potassium salt of indoxyl sulfuric acid. Indoxyl may be present in urine also in combination with glycuronic acid. The observations of Stanford that the indigo-forming substances may disappear if the urine has stood even a few hours, make it necessary to examine freshly voided specimens. In many instances, therefore, the results reported in the literature are of little value. There is no indication that such a disappearance takes

place while the urine is in the bladder. The presence of indican in the urine has been regarded as indicating putrefactive processes in the intestinal canal. As a rule von Reuss[301] found indican absent on the first day of life; it occurred rarely on the second day; in largest amounts on the fourth day, but was frequently present during the following days. The urine for his tests came from breast fed infants. Indican was found in the urine of infants who were developing well, and also in those of infants whose weight curve lagged. It was found, whether the food supply was ample or not, in cases of diarrhea and in cases inclined to constipation. The artificially fed infant excretes indican perhaps more regularly and in larger quantity. Indicanuria in the newborn occurred in about 8 per cent. of 338 examinations made by Bonar. Twenty of the 50 cases showed it at one time or another. It was found most frequently on the third, fourth and fifth day of life and could not be associated with any abnormal clinical findings. Mayerhofer[244] concludes that the clinical value of the indican reaction is very doubtful. This represents the view accepted at the present time. Under such conditions a more detailed discussion of the subject may be omitted. The claim that an increased excretion may be brought about by an abnormal tissue decomposition is not sufficiently founded. Mayerhofer also emphasizes the fact that the excretion of indican does not run parallel with that of other products of putrefaction. This lack of parallelism in the excretion of various substances owing their origin to putrefaction may become of value when more is known about them. Certainly there is every reason for the assumption that the processes of putrefaction are not always the same.

Urobilin.—Urobilinogen and urobilin occur in the urine under certain conditions. Meyer-Betz has given a detailed account of this problem from which the following is taken: Urobilinogen is identical with hemibilirubin, which can be obtained easily from bilirubin in crystalline form. Urobilin is derived from urobilinogen; in contrast to the latter, it is not a definite chemical compound, but a mixture of condensation products. The clinical significance of the urobilinogen and urobilin excretion is the same. The shorter term may be used, therefore, collectively. Urobilin, then, is formed from bile in the intestines by the action of bacteria. With the absence of bile from the intestines, no urobilin is excreted. From the intestines it is carried to the liver where it is removed from the blood entirely or nearly entirely under normal condition. According to this conception urobilinuria is of entero-hepatic origin.

More recently urobilinuria has been associated with retention of bile constituents in blood and tissues. For instance, Adler regards it as the finest indicator for such a retention. The production of bile pigments is not dependent on the liver alone.[97,390,404] Most strikingly has this been confirmed by Mann, Bollman and Magath who demonstrated the formation of bile pigment in the dog after removal of the liver. Wherever bile pigment occurs in the blood, urobilinuria may occur, and it may therefore occur independent of

the intestines or the liver. Brulé and Garban, furthermore, call attention to the fact that the urine of the newborn contains very noticeable amounts of urobilin before feeding, and that it can always be found before the appearance of sterocobilin in the stools. In debilitated breast fed children sterocobilin may be absent until the age of two to four months, although their urine may contain small quantities of urobilin. While the presence of urobilinuria is no longer accepted as necessarily indicating an hepatic lesion, it is often associated with such lesions when it reaches its greatest intensity. A normal person always excretes a small amount of urobilin according to Adler. Tugendreich found it absent from the urine of normal children. Bookman found it in only very small amounts in normal infants, and Ostrowski[285] could only find it in four of twelve healthy infants. In a variety of diseases urobilin is markedly increased. Urobilinuria can occur at times in all of the infectious diseases. Scarlet fever is accompanied by urobilinuria in the great majority of cases. It is less common in cases of measles and diphtheria. In severe cases of acute articular rheumatism it is very pronounced. Of special interest is the urobilinuria in cases of so-called hemolytic icterus and paroxysmal hemoglobinuria, in which the urobilinuria may last much longer than the excretion of the blood pigment. Bookman made the interesting observation of a paroxysmal attack of discomfort occurring in the course of paroxysmal hemoglobinuria, but without the appearance of hemoglobin in the urine. This attack was followed by a marked urobilinuria.

Bile Pigments and Bile Acids.—After icterus neonatorum, bilirubin is rather frequently present in urine for about two months, when it disappears. As in the adult, it appears with icterus, after hemorrhages and during septic diseases. That bile acids occur in the urine under normal conditions is not certain. In cases of icterus they appear.

Diazo-reaction.—The diazo-reaction of Ehrlich is dependent on the presence of substances containing iminazol. The clinical importance of this group of substances is illustrated by one of its members, histidin, and its derivative histamin. The diazo-reaction occurs rather constantly in cases of typhoid and typhus fever, measles and advanced tuberculosis; it often occurs in cases of pneumonia, scarlet fever, diphtheria and erysipelas, and is usually absent in cases of articular rheumatism, meningitis, German measles and chicken-pox. Particularly in cases of tuberculosis, it was thought possible to use the reaction for prognostic purposes, a pronounced diazo-reaction being regarded as a signum mali ominis. One of the later publications dealing with various forms of tuberculosis in children does not sustain such a claim.[344]

Guanidin.—Guanidin compounds have been isolated from the urine of adults in small amounts.[4,95,200] Burns and Sharpe isolated it from the urine of normal children. In parathyroidectomized animals Koch demonstrated a marked increase of guanidin, methyl and

dimethyl-guanidin, and Burns and Sharpe found such an increase in children afflicted with idiopathic tetany, a finding which should be supported by further and more extensive investigations. Guanidin elicits convulsive seizures in animals which can be prevented by the administration of calcium.[164]

Cystin.—Whether cystin is excreted normally is not quite certain, but its occurrence is not associated with any special disease. Its presence in appreciable amounts signifies a peculiar abnormality of the protein metabolism whereby the excretion of other amino acids is perhaps also increased.[408] Looney, Berglund and Graves do not regard cystinuria as an index to a general disturbance of the amino acid metabolism. It is of further interest that the excretion of cystin may be associated with that of leucin, tyrosin and particularly that of the diamins, cadaverin and putrescin,[358] Ackermann and Kutscher describe the presence of lysin. By itself, cystinuria can hardly be called a disease, but it may lead to the formation of stones. Such stones have been found in children as early as the second year. In rare instances cystin has been found outside the genito-urinary system. The organs of a twenty-one and one-half months child were found infiltrated with numerous white points which, in a section of the spleen, proved to be cystin. Cystin has also been found in liver, in muscle, and in blood.[198] Cystinuria frequently runs in families, and whenever cystin is found in one member of a family, it is well to examine the urine of other members. The typical cystin crystals, hexagonal plates, may usually be seen on repeated examination, particularly after acidifying the urine with acetic acid and letting it stand. If this does not occur, the urine may give a very pronounced reaction on boiling with lead acetate and sodium hydroxid. The blackening is due to the formation of lead sulphid by the easily split off sulfur of the cystin. Cystinuria, it must be noted, may be transitory.

Sugar.—The urine of normal adults contains small amounts of sugar.[343] With an improved method of determination Benedict, Osterberg and Neuwirth were able to obtain very interesting quantitative data. Part of the sugar is readily fermentable with yeast, and is in all probability dextrose; another part is not fermentable, and its nature is unknown. Some of the irregularities in the finding of sugar in the urine of infants can be explained by the methods employed in its demonstrations. For instance, in order to obtain a positive test with a copper salt, glucose must be present in a certain concentration. The urine of a number of newborn infants, voided before any food was given, was examined by Millikin, using the method of Benedict and Osterberg.[39] In every case sugar was present. When the urine could be examined for non-fermentable sugar this was also found.* The frequency of sugar elimination by the normal newborn has also been established by Rosenbaum. Using the method of Benedict and Osterberg Greenthal found from 100 to 400

* These cases do not belong to the cases described by Hoeniger as ephemeral traumatic glycosuria of the newborn.

mg. total sugar in twenty-four hour specimens of urine of infants receiving the usual amount of sugar in the diet. The non-fermentable sugar ranged from 45 to 150 mg. Like Benedict, Osterberg and Newwirth, he found that the quantity of sugar excreted is dependent on the intake (Schloss and Harrington[334] in unpublished results reached the same conclusion), and that the increase falls mostly to the share of the fermentable sugar.

Previously reported results were obtained by less delicate methods, and so it was claimed that the urine of healthy infants did not contain sugar, or only rarely, during the first days of life. In children three to twelve years of age, Binet examining the urine voided after the midday meal, usually found sugar. The sugar which appeared at different times in the urine of premature infants fed with human milk and doing well was claimed to be lactose.[279] This dissacharide was also found by Rietschel[306] in case of breast fed infants on resumption of feeding after a few days fast. Under various pathologic conditions, such as febrile diseases, gastro-intestinal disturbances, and particularly alimentary intoxication, sugar may be excreted more readily.[207249,] Its appearance in the urine is provoked by ingestion. The sugar in the urine has been given as lactose, sometimes in association with its split product galactose, and more rarely maltose. Schloss could not find any evidence of excretion of a dissacharide in the urine of infants with severe nutritional disturbances. Lactose was only present in infants who were not thriving, and who were ingesting considerable amounts of lactose. In the other cases the sugar was very probably glucose. Vou Reuss[300] found saccharose when this was given in the food, and Rietschel[305] told of the appearance of levulose after feeding carrot soup. On administration of cane sugar in amounts exceeding the limit of assimilation in infants (more than 8 to 10 gm. for each kilogram of body weight), a mixture of cane sugar, levulose and dextrose seems to have been present in the urine.[269] The time of excretion of reducing substances rarely exceeded four hours. In some cases of eczema a mellituria has been reported by certain authors,[25] but others could not confirm the claim of a decreased sugar tolerance in exudative diathesis.[279, 232] Sugar tolerance has been studied by a number of observers by administrating sugar by mouth in increasing amounts, and determining the dose following which sugar appeared in the urine. The variations of this tolerance are great, and the normal infant can take care of the commonly used sugars to such an extent that a definite glycosuria hardly occurs before the intestinal tract reacts with unmistakable symptoms to the excessive feeding of sugar.[26,101,179, 289,295,379] The experiments of Keller permit the statment that smaller amounts of levulose introduced by mouth lead to its excretion than of dextrose and maltose.* More maltose can be given before its appearance in the urine than lactose. Czerny and Keller object very justly to the method of determining sugar tolerance by feeding. On subcu-

* On intravenous injection Beumer also found that levulose is excreted more readily.

taneous injection Keller found that saccharose and lactose are excreted under conditions which do not lead to the excretion of levulose (fructose), glucose, galactose or maltose. The first subcutaneous injections of lactose which Leopold and von Reuss administered to infants were followed by a complete excretion of the lactose. There are objections to this method of determining sugar tolerance also. Aside from local irritation, which may be produced, the rate of resorption is beyond control. Woodyatt and his co-workers[321,407] introduced the intravenous injection at definite rates. Thus it was found that the normal person excretes glucose when the dosage exceeds 0.8 gm. for each kilogram and each hour, largely independent of the concentration of the solution injected. For infants and childern few data are available as yet. The few approximately normal infants observed by Sauer indicate that they do not differ from the adult. Sauer[239] found that the tolerance of atrophic infants to glucose is markedly increased, and later Beumer[44] found less sugar than normal excreted in intravenous injection in inanition. In these studies the appearance of sugar was determined by a copper reduction test, that is, a certain concentration had to be reached before the presence of sugar in the urine became demonstrable. Benedict, Osterberg and Neuwirth claim that the introduction of glucose leads to a very gradual increase of glucose excretion in the urine, which is normally present, so that there is no such thing as a real glucose tolerance, in other words there is no definite point at which the glucose excretion shows a sudden marked increase. An increased sugar excretion is designated glycuresis. In a series of tests on diabetic patients in the sugar-free state Felsher found a sugar excretion corresponding to that of normal persons, by the method of Benedict and Osterberg.[39] With each increase in the diet and thereby in the available carbohydrate, the sugar excretion may remain unaffected, or show a definite but temporary increase followed by a restoration to the former level, or a slight rising tendency may be present. When a certain level is reached, any further addition to the diet leads to a rapid, even sudden acceleration of the sugar excretions, out of proportion to any which have occured before. At least under certain conditions a "tolerance limit" for glucose seems to exist. The whole problem of sugar tolerance, not only for infants and children, needs further elucidation. The fact that more or less sugar may be excreted after ingestion of relatively large amounts of sugar does not mean that such a glycosuria is injurious. Intravenous injections of large amounts of sugar produce an intense diuresis, and if pushed too far, may lead to very serious consequences.

The determinations of sugar tolerance by feeding, in the manner in which they have usually been conducted hitherto are of very limited value, and since the tolerance tests with levulose made with the purpose of testing the functional activity of the liver do not satisfy the demands now required of such tests, they need not be discussed here. Alimentary galactosuria after administration of lactose, has been described in various diseases, particularly in icterus catarrhalis.[154,255]

The excretion of sugar in cases of diabetes mellitus is considered in connection with this disease.

Pentoses have been found in the urine of children. De Bruin reports its occurrence in two brothers six and eight years of age, whose father also excreted pentose. From the urine of a five-year-old boy, Aron[21] obtained the osazone of dl-arabinose.

Glycuronic Acid.—Glycuronic acid is commonly present in the urine of adults. The conditions under which it appears in the urine of infants have been studied more recently by Mayerhofer.[243] Its appearance is ascribed to intestinal putrefaction, of which it is supposed to be a more delicate test than indican, which appears later. It is absent from the urine of the normal breast fed infant, while in artificially fed infants it may be present in large amounts, even when they are doing well. The urine of the newborn, voided before the first feeding, gives a positive reaction, introducing the possibility that other than putrefactive processes may yield glycyronic acid, a possibility to which the formation of camphoglycuronic acid on subcutaneous injections of camphor also points very strongly. In even slight enteral and parenteral disturbances (fever), the glycuronic acid reaction of the infant's urine becomes positive, or is increased. The glycuronic acid does not occur in the free state in all probability, but combined with other substances, such as phenol, cresol and indoxyl. After the administration of camphor or menthol these substances are excreted in combination with glycuronic acid. The excretion of campho-glycuronic acid may be delayed in cases of severe nutritional disorders.[340] The administration of chloral hydrate gives rise to the formation of chloraluric acid, which is a combination of glycuronic acid with trichlorethylalcohol derived from chloralhydrate. The introduction of benzoic and salicylic acid may lead to the excretion of benzoic and salicyl-glycuronic acid, while the greater part of these acids combine with glycocoll to form hippuric or salicyluric acid. The excretion of campho-glycuronic acid after oral administration of cadechol, a preparation containing 17 per cent. camphor, was diminished in one child with catarrhal icterus, one with stasis of the liver due to pericarditis, and one with tuberculosis.[154]

Volatile Fatty Acids.—Normal urine from adults contains volatile fatty acids, particularly formic, acetic and butyric acids. Acetic acid occurs in the organism, entering in the composition of chondroitin-sulfuric acid. Only a few determinations have been carried out with urine of infants. Soldin obtained from the urine of breast fed infants an average amount of acid equivalent to 9.7 c.c. of N/10 alkali, the urine of artifically fed infants yielded an equivalent of about 25 to 104 c.c. with an average of about 55 c.c. of N/10 alkali. The largest amounts were found on a diet of buttermilk, less on cow's milk, and the least on malt soup. Aron and Franz found in ten cases a daily output varying from traces to about the equivalent of 10 c.c. of N/10 alkali. In two instances (same case) the acids neutralized more than 10 c.c. N/10 alkali, in seven cases, less than 5 c.c.

The presence of formic acid in the urine of a number of infants was demonstrated by McNeal and Eldridge. Dakin, Janney and Wakemann give about 30 to 119 mg. as the daily excretion of man on a mixed diet, with an average of about 60 mg. The administration of methyl alcohol increases the formic acid excretion (Authenrieth and others).

Lactic Acid.—Whether any of the higher fatty acids are excreted in the urine has not been determined. Dextro-rotatory lactic acid (sarcolactic) is also a normal urinary constituent. Its amounts are given by von Fürth, Ishihara and Ryffel as about 6 to 8 mg. for each 100 c.c. urine. Maver, using the method of Ryffel, found lactic acid in a few normal children and in patients from one to eight years of age. The 24-hour excretion varied from 6.3 to 84 mg., the latter in a case of endocarditis. A considerable number of cases, including infants less than one year old, were omitted from her publication because the collection of urine was not complete. Lactic acid was always present. In children suffering from various ailments, including athrepsia, 6 to 38 mg. lactic acid was found by Clausen with the aid of an improved method. Underhill and Steele found 0.56 gm. of zinc lactate in the urine of a boy, two and one-half years of age, during an attack of recurrent vomiting. Increased excretion of lactic acid may be expected in conditions which interfere with oxidative processes in the tissues.

Oxalic Acid.—Aron and Franz missed oxalic acid only once in their examination of the urine of 17 infants. Sedgwick[349] found that newborn infants excrete varying amounts of oxalic acid up to 9 mg. a day, and a two-year-old about the same. A six-year-old child excreted an average of about 22 mg. each day. In the latter case the excretion dropped to about 16 mg. on a diet free from oxalic acid, going on the last day as low as about 6 mg. On the addition of rhubarb, which is relatively rich in oxalic acid, the excretion rose to about 33 mg. The amount excreted by the adult normally varies from a few milligrams to about 20. Besides rhubarb, spinach and other vegetables contain oxalic acid and it is also present in cocoa and tea. While some of the oxalic acid excreted in the urine may be derived from that contained in the food, there is no doubt that some of it, and perhaps the greater part, is of endogenous origin. Cases of "oxaluria" were thought to be characterized by an increased excretion of oxalic acid. The important feature of oxaluria lies in the constancy of the sediment formation (calcium oxalate), even on diets poor in oxalic acid. Of clinical importance is the danger of stone formation.[81]

Succinic Acid.—The presence in urine of another dibasic acid, namely succinic acid, has been claimed. There are reasons to suspect its occurrence under certain pathologic conditions. Convincing proof of its occurrence has not been brought.

Citric Acid.—Citric acid is a tribasic acid. It occurs in the urine of adults, children and infants normally.[13, 14, 226] A perfect quantitative method has not been worked out as yet.[223] It is reported that

normal adults excrete between 0.4 and 0.5 gm. a day. In children, aged from 6 months to 14 years, the excretion varied from 30 to 431 mg. The occurrence of the acid is not dependent on its occurrence in the food.

Alkaptonuria.—Homogentisic acid is the aromatic acid (dioxyphenyl acetic acid) to which the urine in cases of alkaptonuria owes its peculiar properties. This urine becomes brown on standing, and becomes rapidly brown or even black on the addition of alkali. It reduces alkaline copper solutions very strongly, but is optically inactive. Sometimes the urine is brown when voided, and stains the cloth. Alkaptonuria belongs to those conditions described by Garrod as "inborn errors of metabolism." In some cases it is undoubtedly congenital, as in the infant reported by Bilderback, and it has been observed in sisters and brothers. The anomaly in itself is of no injurious consequence. The homogentisic acid is probably a product of the normal intermediary metabolism, which in these individuals escapes further changes. The aromatic radicals of food or organ proteins may serve as its sources. The alkaptonuric individual transforms tyrosin and phenylalanin to homogentisic acid,[274] and excretes the latter when administered quantitatively. (For the relation of alkaptonuria to ochronosis see Gross and Allard; for literature on alcaptonuria, Pincussohn.)

Acetone Bodies.—The so-called acetone bodies which occur in urine are acetone, diacetic and B-hydroxybutyric acid. Engel[94] gives 7 to 17 mg. acetone as the daily excretion of the adult. Magnus Levy puts it at 10 to 30 mg. in the urine, and 30 to 80 mg. in the expired air. Mayerhofer states that the presence of acetone can usually be demonstrated in the urine of newborn infants receiving barely sufficient, or insufficient food. Newborn infants, kept on weak tea and saccharin, excrete acetone bodies after about 50 hours; after 72 hours they become abundant.[327] More pronounced excretion particularly of diacetic acid and hydroxybutyric acid has not often been found in the newborn infant. Seham reports that in ten cases practically no acetone was found. More extensive work seems necessary in order to reach a definite conclusion. The normal infant excretes acetone. The data given for acetone usually include, besides the preformed acetone, that derived from diacetic acid.

Meyer and Langstein put the acetone excretion of the normal infant at 1 to 4 mg. The figures of Liefman fall also within these limits. Besides acetone, Schlossmann and Murschhauser found B-hydroxybutyric acid. The urine of 21 infants and children from 2 months to 12 years of age, reported by Veeder and Johnston,[392] contained 7 to 110 mg. acetone from acetone and diacetic acid each day. The lowest and the highest amounts were obtained in cases of chronic valvulitis. The majority of infants excreted between 10 and 40 mg. The B-hydroxybutyric acid expressed as acetone varied from 3 to 66 mg. Only one infant excreted less than 10 mg., and few exceeded 50 mg.

Meyer and Langstein demonstrated an increase of the acetone excretion in fasting, observations which were confirmed and amplified with the inclusion of B-hydroxybutyric acid by Schlossmann and Murschhauser as well as by Veeder and Johnston. The acetone bodies of the artificially fed infants serving for the observations of Schlossmann and Murschhauser were increased during hunger about three times more than those of a breast fed infant. The increase of the acetone bodies in hunger is on a par with that observed in carbohydrate abstinence. Among the children observed by Veeder and Johnston,[393] a well nourished infant, 18 months old, increased its acetone excretion from about 0 1 to 0.5 gm., and its acetone derived from B-hydroxybutyric acid from about 0.4 to about 3.9 gm. in hunger. The greatest absolute amounts were excreted by a boy 10 years old, who eliminated about 1.3 gm. of acetone and 4.9 gm. B-hydroxybutyric acid as acetone. As usual, under such conditions, the amount of B-hydroxybutyric acid exceeds that of the other acetone bodies considerably. These amounts are greater than those given by adults on prolonged fasting. It is generally conceded that children respond under various conditions more readily with an acetonuria than adults, and excrete actually more acetone bodies.

In a number of cases Jeans and Johnston examined the urine of children who had undergone surgical operations under ether anesthesia. In some of these they found a marked increase of the acetone bodies. It is a well established fact that the acetone excretion in the urine may be much increased in fevers The various factors which may determine this increase are not well understood. According to Veeder and Johnston[394] this need not always take place; it is not dependent on the severity of the infection, nor the degree of temperature; neither can it be explained by a decreased intake of food. Whether variations in the amount of acetone given off by the lungs play a part has not been determined. It is known that acetone is excreted through the lungs, and according to Langstein and Meyer the child may excrete more acetone through the lungs than through the kidney. Von Gaizler found acetone in all severe cases of burning with lye. In cases of recurrent vomiting the acetone bodies are increased in the urine, an increase which has been observed before the onset of the attack. The excretion of the acetone bodies in diabetes mellitus will be considered elsewhere. An increased excretion of acetone bodies has been regarded as a sure sign of acidosis. Howland and Marriott emphasize the fact that acetonuria and acidosis are not synonymous.

Glycerin.—It is surprising that normal urine should not contain any glycerin.[100] Whether it occurs at all in the urine of infants and children normally, or under pathologic conditions is not known.

Phenols.—Besides volatile fatty acids, urine contains other volatile substances. Of these, the phenols (phenol and cresol) are known sufficiently to be dealt with. A part of these substances is excreted in combination with sulphuric acid (compounds such as indoxyl and perhaps skatoxyl, sulphuric acid; the so-called conjugate

sulphates), and a part is combined with glycuronic acid. Folin and Denis demonstrated the presence of free phenols. The phenol determinations previously made represent the sum of free and conjugated phenols. Even so, the methods employed may entail considerable loss, which is avoided by the colorimetric method of Folin and Denis.* [107] In certain normal men and women the total phenol excretion for each day amounted to from 0.29 to 0.48 gm. A 15-year-old boy excreted 0.28 gm., one 11 years old, 0.24 gm., one seven years old, 0.18 gm., and a three-months-old normal infant 0.05 gm. With the older methods Meyer[248] found in two breast fed infants 2.5 to 5.9 mg. phenol each day, and five infants from seven weeks to 13 months of age artificially fed and not well developed, excreted about 8 to 17 mg. The figures of Soldin fall within the limits of those of Meyer. Moore used the method of Folin and Denis. The urine of 19 newborn infants was collected for a period of three days. It always contained phenol, the total varying from about 2 to 23 mg. These infants were put to the breast every four hours after the first half day. The average amount of phenol was about 11 mg. Of the 15 infants, one week to six months of age six were entirely or almost entirely breast fed. The averages of the determinations, of which a considerable number were made in several cases, were from 9 to 37 mg. for the breast fed infants. The averages for the artificially fed infants were about 17 to 58 mg. total phenol. The determination of Folin and Denis obtained from seven infants under one year of age, sick and well, yielded from 35 to 68 mg. Moore confirmed the observation that an increase in the number of stools decreases the output of phenol. But more important, Folin and Denis[108] found that with an increase of the protein in the food, the phenol excretion is increased. Three illustrative cases are given (Table 19).

Table 19.—Phenol in Urine (Folin and Denis[108])

Case	Total nitrogen of urine, grams	Total phenols, grams
1	7.6	0.32
	7.2	0.25
	16.0	0.48
	15.0	0.49
2	7.2	0.20
	20.0	0.45
3	4.5	0.16
	22.0	0.36

* Tisdall states that the method of Folin and Denis yields results which are too high.

The averages calculated by Moore for his breast fed and artificially fed infants gave these results:

	Total nitrogen, grams	Total phenols, grams
Artificially fed	1.6	0.337
Breast fed	0.4	0.173

The comparison of the single determinations offers too many divergent results to accept unreservedly the rule of Moore that trebling the protein intake doubles the phenol excretion. On an average, the breast fed infant excretes less phehol for each kilogram of body weight than the artificially fed.

The method of Folin and Denis[107] permits a determination of the total as well as of the free phenols, so that the conjugated phenols can be calculated. Free phenol exceeds, as a rule, the conjugated phenols markedly. In the newborn infants of Moore the free phenol constituted, on an average, 76 per cent. of the total, and in the older infants 83 per cent. The average output of the children observed by Folin and Denis was 89 per cent. free phenol, and in two cases all the phenol was excreted as free phenol. In three normal infants (Utheim) three and one-half and seven months of age the total phenol output was about 36, 73 and 40 mg. and the free phenol made up 78, 59, and 66 per cent. In nine athreptic infants, one and one-half to 18 months of age, the total phenol excretion amounted to from 21 to 41 mg., and the percentage of free phenol fluctuated between 41 and 82. Three other infants not normal, but doing well, aged eight and 10 months, excreted 51, 54 and 72 mg. total phenol with 44, 65 and 100 per cent. free phenol. A certain part of the phenols may possibly be produced in the intermediary metabolism, but the main part seems to be referable to putrefactive processes in the intestines, leaving out of consideration cases in which phenol as such enters the organism, or in which it arises from the decomposition of such drugs as salol. The phenols are derived from the tyrosine group of proteins, while indican is derived from the tryptophane group. As Folin and Denis[108] point out, although both owe their origin to putrefactive processes, their production and elimination need not and do not run parallel. Benzol administered by mouth leads to an increase of the phenol excretion. In cases of athrepsia, the power of the organism to oxidize benzol to phenols diminished. This was first shown by Freund, and recently on a larger scale by Utheim. The normal infant increased the phenol output by 60 to 155 mg. in 24 hours following the administration of 0.5 mg. benzol, while in the athreptic infant the increase did not reach 36 mg.

Conjugated Sulphates.—Inasmuch as the aromatic group of the conjugated sulphuric acids owe their origin preponderantly to putrefaction, their production can be influenced by measures counteracting

these. The amount of conjugated sulphuric acids excreted by the adult varies between 0.1 and 0.3 gm. Senator found small amounts in the urine of the newborn. The three normal breast fed infants observed by Freund,[111] two, two and one-half, and four and one-fourth months old, excreted an amount of conjugated sulphuric acid equivalent to about 9, 13 and 16 mg. barium sulphate. Meyer's[248] six-months-old infant excreted about 12 mg.; two infants observed by Soldin, aged four weeks, about 10 mg.; a convalescing infant, when three weeks old, excreted 16 mg., and six weeks later about 5 mg. The case reported by Amberg and Morrill, an infant aged one month, averaged about 13 mg. Thirteen artificially fed infants observed by Freund,[111] from nine weeks to nine months of age, and far from being normal, excreted from 16 to 137 mg. The highest amounts were not obtained from infants with foul smelling stools. The infants observed by Meyer, from seven weeks to eight months of age, excreted between 16 and 35 mg., and the infants of Soldin who were developing well, between 12 and 20 mg. In three cases of Soldin's the infants were markedly underweight, and excreted 11 to 90 mg. conjugated acids expressed as barium sulphate. The infant observed by Talbot and Gamble was about six months of age. The average excretions of the three-day periods were 38 to 81 mg., the latter on an insufficient diet. Otherwise the variations were from 38 to 52 mg. Czerny and Keller cite reports from Gallo de Tomasi and Ponticaccia. Gallo de Tomasi found an average excretion of 78.5 mg. (maximum 147, minimum 37 mg.) in children from four and one-half to seven years of age, on a mixed diet. On a milk diet the conjugated sulphuric acids always decreased, and dropped as low as about 8 mg. A diet rich in carbohydrates had the same effect, while a meat diet increased the excretion of the conjugated sulphates. Ponticaccia studied the excretion of four healthy children, from four to six years of age on a mixed diet. The average excretion was 101 mg., with variations from 75 to 135 mg. Schwartz[346] observed four children two and one-half to five years of age, with an average excretion of 16 to 23 mg on a diet free from meat. The relation of the conjugated sulphuric acids to the other sulphates will be taken up later.

Organic Phosphorus and Chlorine Compounds.—A certain amount of phosphorus may perhaps be excreted in organic combination; if so, it is not definitely known in what form, as is also true of the organic chlorine compound which is supposed to be excreted in the urine.*

* In order to gain some general information concerning the total output of organic substances Mayerhofer[213] introduced the permanganate reduction index, which denotes the number of cubic centimeters of one-tenth normal potassium permanganate solution which is used up by 1 c.c. urine on boiling ten minutes with 60 c.c. of 4 per cent. sulphuric acid. Mayerhofer says that his material is not sufficiently large to permit the establishment of normal values. Breast-fed infants have a lower reduction index than the artificially fed. In the breast fed infant a rise of the index may be the earliest indication of impending disturbance.

Carbon-nitrogen and Caloric-nitrogen Ratio.—If all the organic substance eliminated in the urine appeared in the form of urea, the carbon-nitrogen ratio would be that of urea $CO\frac{NH_2}{NH_2}$. Carbon-nitrogen, participating in the weight of any quantity of urea in proportion of their atomic weights, the $\frac{C}{N}$ is $\frac{12}{2 \times 14} = 0.43$. The carbon-nitrogen ratio of urine is obtained by determining the total amount of carbon and of nitrogen in grams, and then dividing the amounts for carbon by those for nitrogen. Substances containing more carbon in relation to nitrogen than urea increase the result, substances containing less diminish it; ammonia, for instance, contains no carbon, and obviously gives zero. The presence of organic compounds without nitrogen, such as sugar, raise this ratio very markedly, nitrogen of course, never being absent from urine. Utheim found for the normal baby, whether breast fed or not, a carbon-nitrogen ratio of 0.64 to 0.77. The ratio for the normal adult is 0.67 to 1.0. Of ten determinations in four athreptic infants only one infant (one determination) had a carbon-nitrogen ratio not exceeding 1, the highest was 2.3. The caloric-nitrogen ratio is obtained by dividing the large calories, determined with the bomb calorimeter, by the total nitrogen in grams, calories and nitrogen being calculated for the 24 hour urine. The caloric-nitrogen ratio for the normal adult is about 7 to 9, for the normal infant about 6 to 10. In acute diarrheas, malnutrition and athrepsia this ratio may be increased. The highest ratio found was about 24. These results suggest the excretion of unfinished or unusual metabolites in athrepsia.

Inorganic Constituents.—Sulphur.—The sulphur of the urine is derived under normal conditions from the sulphur of the proteins, those of the food and those of the organism. It is excreted in the form of sulphates, and in a non-oxidized or so-called neutral form. The oxidized sulphur is divided in two parts, one the so-called inorganic sulphates, the other the conjugated sulphates. The neutral sulphur may also be subdivided in several fractions; they are of no further interest here. A part of it occurs in organic combinations, another part in inorganic, such as rhodanates. The various forms in which the neutral sulphur appears in the urine are not known. Of interest is the easily split off sulphur, which is the cause of the blackening when urine is boiled with lead acetate and sodium hydroxid. This reaction, as has been stated, is always suggestive of cystin, particularly in a protein-free urine. The inorganic sulphates constitute, as a rule, the bulk of the sulphur excreted in the urine. Their amount expressed as barium sulphate is about 4 to 9 gm. a day in the adult on a mixed diet. It is very dependent on the protein intake. The conjugated acids vary mainly with processes of intestinal putrefaction. The excretion of neutral sulphur is much less dependent on the protein intake, and is probably more intimately connected with the endogenous protein metabolism. On a transition from a diet rich in protein to a

diet poor in protein, Folin states that the inorganic sulphates decrease absolutely and relatively, that is in percentage of the total sulphur, while the neutral sulphur remains constant absolutely, but increases relatively. The conjugated sulphates decrease absolutely but increase relatively. At first it was thought that the relation of neutral sulphur to the inorganic sulphates permitted a conclusion as to the oxidizing power of the organism. When it was recognized by Benedict that the excretion of the inorganic sulphates was largely dependent on protein intake, while that of the neutral sulphur was much less so, this relation of the neutral sulphur to the oxidized sulphur lost considerable of its importance.

In hunger Cathcart found a decrease of the neutral sulphur, but very little when compared with the drop in inorganic sulphates. Nevertheless, changes in this relationship may perhaps become very significant under certain conditions. This is suggested by the study of Richards and Wallace on the influence of potassium cyanid on protein metabolism. It has been generally accepted that cyanids depress the oxidative powers of the cell. In severe cyanide poisoning, the neutral sulphur was increased at the expense of the inorganic sulphates. In certain pathologic conditions the excretion of neutral sulphur has been found to be markedly increased. In severe cases of pneumonia, on a non-nitrogenous, but calorically sufficient diet the amount of neutral sulphur was increased from six to eight times over that found in normal persons.[202] The excretion of large quantities of nitrogen (30 gm.) showed extensive breaking down of tissue. Increase of neutral sulphur has also been reported in cases of diabetes and carcinoma. It had been reported in cases of arsenic and phosphorus intoxication, and in other conditions leading to an extensive breakdown of body tissue (Benedict).

The number of investigations dealing with the sulphur excretion in infancy and childhood is restricted.

The table of Freund[111] contains three normal breast fed infants two to four and one-fourth months of age, in whom the total sulphur as barium sulphate was 254, 255 and 448 mg., the neutral sulphur being 118, 138, and 231 mg. In seventeen other infants, up to eleven months of age, the total sulphur varied from 287 to 1293 mg., and the neutral sulphur from 76 to 356 mg. On the whole, the higher neutral sulphur was associated with the higher total sulphur. The babies were much below par, and the results do not permit conclusions.

The daily excretion of sulphur expressed in milligrams of barium sulphate by a breast fed infant about one month of age, was reported by Amberg and Morrill[15] (Table 20).

TABLE 20.—DAILY EXCRETION OF SULPHUR BY AN INFANT ONE MONTH OLD (AMBERG AND MORRILL[15])

	Protein of food for each kilogram of body-weight, grams	Total sulphur	Total sulphuric acid	Neutral sulphur
A	2.8	330	182	147
B	2.5	282	178	103
C	2.3	...	216	
E	...	319	239	80
F	0.9	258	185	73
G	0.7	208	130	77
H	0.7	273	137	136

The average daily excretion of barium sulphate by an infant, about six months of age, and artificially fed, observed by Talbot and Gamble, is shown in Table 21.

TABLE 21.—AVERAGE DAILY EXCRETION OF BARIUM SULPHATE BY AN INFANT SIX MONTHS OLD (TALBOT AND GAMBLE)

	Protein of food for each kilogram of body weight, grams	Total sulphur, milligrams	Inorganic sulphuric acid, milligrams	Conjugated sulphuric acid, milligrams	Neutral sulphur, milligrams
1	2.3	551	322	81	148
2	4.4	998	740	44	215
3	4.8	1241	1053	38	151
4	5.9	1349	1122	44	183
5	7.1	1969	1717	52	174

This case illustrates very well the rather marked uniformity of the neutral sulphur compared with the pronounced increase of the sulphuric acid on increase of the protein intake.

For the adult Folin[105] gives the following amounts (calculated as for barium sulphate).

	Diet rich in protein		Diet poor in protein	
	Grams	Per cent.	Grams	Per cent.
Total nitrogen of urine	16.8	....	3.6	
Total sulphur	10.56	....	2.2	
Inorganic sulphuric acid	9.48	90.0	1.33	60.5
Neutral sulphur	0.52	4.8	0.58	26.3

The cases of Schwartz[346] are (1) a normal boy, aged five years, weighing 23.5 kg. and three male rachitic dwarfs; (2) a child, aged five years, weighing 10.7 kg.; (3) a child, aged two and one-half years, weighing 9.4 kg., and (4) a child, aged five years, weighing 13.9 kg. The diet was free from meat, the protein being supplied chiefly by milk and eggs. The protein for each kilogram is calculated roughly. The periods of observation lasted seven days. The figures give the sulphur in milligrams for barium sulphate.

TABLE 22.—SULPHUR EXCRETION (SCHWARTZ[346])

	Protein of food for each kilogram, grams	Total sulphur, milligrams	Total sulphuric acid, milligrams	Neutral sulphur, milligrams	Conjugated sulphuric acid, milligrams
1	2.5	559–627	512–575	37–52	11–45
	Average	592	546	46	23
2	3.8	320–391	258–340	28–131	5–28
	Average	356	281	68	19
3	4.0	298–397	253–334	32–95	8–24
	Average	345	289	56	14
4	3.6	432–543	430–887	12–49	11–34
	Average	488	524	36	22

A discussion of the sulphur excretion in its different forms under various conditions must be left open.

Phosphorus.—Phosphorus is present in urine chiefly in the form of salts of phosphoric acid. It has been contested that it is not present in any other form, at least under usual conditions. The phosphates are supposed to determine largely the reaction of the urine, the monobasic salts being relatively preponderant in acid and dibasic salts in alkaline urine. As a rule more phosphoric acid is excreted by way of the kidneys than in the stool. The amount of acid excreted in the urine depends on the intake of phosphorus and on the catabolic processes. The latter can furnish very significant quantities even in the absence of food. For instance Keller's[189] experiments on himself gave on four successive days of fasting about 1.9, 2.4 and 2.5 gm. phosphorus expressed as P_2O_5. An artificially fed infant, 11 months of age, who was fasted for therapeutic reasons, excreted about 200 to 370 mg. On whole milk it excreted later 2 gm. The subject studied by Cathcart excreted before fasting 3.7 and 4.1 gm. phosphorus as P_2O_5 each day, and on successive days of fasting 2.3, 2.9, 3.0 and 2.9 gm.; from then on to the fourteenth day it dropped to 1.3 gm. The observations

of Gamble, Ross and Tisdall[124] on children also show that it may take several days fasting before a definite decrease of the urinary phosphates becomes noticeable.

Langstein and Niemann found in three normal, breast fed newborn infants a daily phosphoric acid excretion of from 26 to 138, 9 to 120, and 8 to 28 mg. during the first week. These cases were observed for 10 days and for the balance of the time the excretion was from 26 to 47, 60 to 72, and 13 to 38 mg. On the first day of life the excretion may be very low. Schloss and Crawford determined the phosphoric acid excretion in four cases in successive three-day periods. The daily average for the first period was about 18 mg.; during the second period there were only traces in three cases, and one averaged about 9 mg. During the third period, there was a trace in one case; the average daily excretion in the others was below 5 mg. The daily average of Michel's infants 5 to 15 days of age was 22, 21, 25, and 34 mg. The six months old infant observed by Lade excreted about 19, 22, 24, 11, 12, 42 and 11 mg. P_2O_5 in 24 hours. The excretion of 42 mg. falls in a period when the weight decreases. The following table taken from Muhl illustrates the excretion of phosphoric acid in the urine of infants fed on human milk. The amounts represent 24 hour averages in mg. P_2O_5 for periods extending over several days. The output in the feces is given in this instance:

Table 23.—Excretion of P_2O_5 by Breast Fed Infants (Muhl)

Author	Age, months	Body-weight, kilo-grams	Daily gain, grams	Intake	Output	
					Urine	Feces
Muhl	2.33	5.49	14	0.251	0.071	0.059
	2.5	5.56	18	0.261	0.094	0.057
	3.75	5.14	18	0.289	0.117	0.048
Tobler and Noll	2.5	4.00	24	0.210	0.057	0.034
Lindberg	2.5	4.29	10	0.294	0.046	0.055
		4.37	23	0.289	0.088	0.062
Michel-Perrett	3.0	4.73	19	0.268	0.075	0.072
Malmberg	3.5	5.45	45	0.359	0.071	0.077
		5.44	37	0.323	0.062	0.036

In the premature infants, three weeks to four months of age, observed by Hamilton, the urinary P_2O_5 varied from 6 to 82 mg. on an intake of 119 to 255 mg. Here the fecal output was from 14 to 30 mg.

Moll noted in four normal infants within the first two months of life, the daily P_2O_5 excretion as follows: No. 2: 12.5, 10.9, 12.0, 27.9 mg.; No. 3: 9, 10.5, 11.3 and 14.5 mg.; No. 5: 24, 29.6, and 42.8 mg.

and K. Josef 78 mg. These seem to be all the examinations made of 24 hour collections of urine, and on these observations, Moll bases his statement that, as a rule, the healthy breast fed infant excretes from 10 to 20 mg. P_2O_5 in 24 hours. These amounts can hardly be accepted as standard. Moll concludes that when a breast fed infant is doing well, is gaining in weight steadily, does not show any signs of disease, and excretes no phosphates in the urine, or only traces, it is healthy. When a breast fed infant loses weight and on an insufficient amount of food has no phosphates in the urine or only traces, hunger alone is responsible for the loss of weight. When a breast fed infant does not gain in weight, or loses weight and on an apparently sufficient amount of food excretes much phosphates, it is suffering from disordered nutrition.*

Slight degrees of dyspepsia yield a urine poor in phosphates while the severely ill infant excretes urine rich in phosphates. If withdrawal of food in a case of acute enteritis for one or two days leads to a pronounced reduction of the phosphates, the prognosis may be regarded as good. The sooner the phosphates drop, the better. If the phosphate excretion is not markedly influenced, the outlook is bad. The conclusions of Moll cannot be accepted in toto since Weidmann examined dyspeptic breast fed infants and found the urine rich in phosphates in 23 per cent., poor in phosphates in 33 per cent., and free from phosphates in 44 per cent. of his cases. Moll's deductions cannot be transferred to the artificially fed infant.

In artificially fed infants Knox and Tracy were unable to establish a relationship between the amount of urinary phosphates and the severity of the disease. Kaminer and Mayerhofer conclude that the phosphate titration of the urine of the bottle fed infant is of very limited value. The phosphates may increase, if transitorily, in enteral and parenteral disturbances, or with changes in the food.

Keller[188] determined the excretion of phosphates in a number of infants, three to eleven months of age. In forty-six breast fed infants it varied between 25 and 142 mg. P_2O_5 daily, the majority of the figures falling between 50 and 100 mg. In the same number of artificially fed infants, the excretion was from 155 to 506 mg.† These figures

* Moll tested urine in 10 and 50 c.c. samples, finding that testing 10 c.c. samples is sufficiently accurate for his purposes. When the addition of 1 to 2 drops of an uranium acetate solution of which 1 c.c. corresponds to 0.005 gm. P_2O_5 to 10 c.c. urine renders it permanently green, the urine contains so little phosphates that it is called free from phosphates. One-tenth cubic centimeter of uranium solution would correspond to 0.5 mg. P_2O_5. The urine is called poor in phosphates when 10 c.c. require 0.3 to 1 c.c. uranium solution, and rich in phosphates when it requires more than 1 c.c. It is somewhat doubtful whether from samples of urine taken at random one can draw conclusions regarding the daily output. If there are no special reasons for so doing, it would appear much safer to determine the daily output. The determinations recorded in Tables 1 and 2 of Moll show that determinations of samples might be very misleading. In any event, while the procedure advocated by Moll may have great advantages it needs better support.

† In the athreptic infants reported by Utheim the excretion did not exceed 540 mg.

are not given as physiologic, because the infants were not well. Nevertheless the discrepancies are sufficiently pronounced to conclude that the artificially fed infant excretes more phosphorous than the breast fed, and that this difference is greater than can be accounted for by the difference in the phosphorous of the food. These conclusions have been confirmed by later observations.

Koeppe emphasizes the influence of the food on the phosphate excretion, concluding that on equal quantities of food, the amount of phosphoric acid varies with the kind of food, and that on the same kind of food it varies with the amount of food. His investigations concerned two infants who were studied for a long time with various changes of food (Table 24).

Table 24.—Influence of Food Intake on P_2O_5 Excretion (Koeppe)

Author	Infant	Quantity of food in 24 hours, grams	Whole milk, grams	P_2O_5 in 24 hours, milligrams
Keller	IX	996 whole milk	996	833
Koeppe	Paul K. I	950 whole milk	950	682
	Fr. St. I	840 whole milk	840	497
	Paul K. II	950 two-thirds milk	633	572
	Fr. St. II	840 two-thirds milk	560	436
Keller	XII	967 two-fifths milk	387	411
	III	600 one-half milk	375	347
	I	640 one-third milk	245	317

The larger amounts of phosphates excreted by older children could be easily explained in this manner. Furthermore, Koeppe deduced an influence of the fat content of the food, so that the higher fat content is associated with a decrease of the phosphoric acid excretion. He cites in this connection the breast fed infant observed by Moll, who decreased its phosphoric acid excretion when it received a milk richer in fat. But in Case XVII, Table 1, Moll describes another infant whose phosphoric acid excretion decreased when it received milk poorer in fat. Both infants did not do well at the time the phosphoric acid excretion was high. In the case of Lindberg, on the addition of fat of human milk to human milk, 102.4 mg. and 91.9 mg. P_2O_5 were excreted against 46.4 and 87.5 mg. without this addition. In the experiment of Muhl a decided difference between high and low fat is not evident. Furthermore some of Keller's cases are called to aid (Table 25). Such observations cannot decide the question raised by Koeppe, whether fat decreases the urinary phosphates, one way or the other.

TABLE 25.—INFLUENCE OF FAT INTAKE ON P_2O_5 EXCRETION (KELLER[188])

		Nitrogen in urine, milligrams	P_2O_5, milligrams	Approximate ratio of phosphorus to nitrogen
1	Skim milk	1149	303	1:4.0
	Cream	545	253	1:2.0
2	Cream	529	281	1:2.0
	Skim milk	2686	480	1:5.5
	Cream	559	247	1:2.5
3	Cream	755	359	1:2.0
	Skim milk	3071	735	1:4.0

Keller remarked that the relative phosphoric acid excretion, that is the phosphoric acid in proportion to the nitrogen in the urine, is lower on skim milk than on cream. Koeppe sees in Keller's absolute figures proof that fat decreases the phosphoric acid excretion. The very pronounced differences in the amount of nitrogen in the urine, the amount of food not being given, suggests that other factors may enter into consideration in these cases, perhaps even preponderantly. It must be kept in mind that we do not possess sufficient information about the factors determining the distribution of the phosphoric acid excretion between urine and feces.

The proportion of the phosphoric acid to the nitrogen in the urine is smaller in the breast-fed infant. In the cases of Keller, the limits are 1 3 6 and 1:11.6, in a decided majority more than seven parts of nitrogen being excreted for each part of P_2O_5. In the cases tabulated, this proportion varied between 1:6 and 1:11. The artificially fed infants of Keller differed from 1:1.2 to 1:4. The results of other investigators were rarely below 1:4.

The phosphorus in organic combination in the urine of adults has been given from 3 to 120 mg. P_2O_5. Keller found in three healthy infants about 6 to 8 mg. The amounts for the thirteen infants, two to ten months of age, were about 2 to 17 mg. forming from 0.5 to 10 per cent. of the total phosphoric acid. In the adult the percentage lies between 1.6 and 4.8.

The starving organism also is said to excrete a small percentage of its phosphorus in organic combination. Moll could find only organic phosphorus in infants severely ill. It has been claimed that, under usual conditions, phosphorus in organic combination does not occur in urine.

The data given by Sherman and Hawley illustrate the influence of the phosphoric acid intake on its excretion. In these cases the fecal output is also registered (Table 26). The phosphoric acid excretion in the older child is summarized in Table 27.

TABLE 26.—INFLUENCE OF P_2O_5 INTAKE ON ITS EXCRETION (SHERMAN AND HAWLEY)

Sex	Age		Weight, kilogram	Period, days	Milk, cubic centimeter	Intake, gram	Output	
	Years	Months					Urine, gram	Feces, gram
F	3	7	16.2	9		2.40	1.25	0.84
M	3	3	15.2			2.40	1.20	0.78
F	4	7	29.5			2.45	1.10	1.20
M	6		21.4			2.85	1.50	1.04
F	6		19.1			1.95	1.25	0.47
F	7		25.2			1.25	1.20	0.73
F	8		39.3			1.85	1.15	0.48
F	9		33.0			2.35	1.05	0.87
F	10		35.4			3.20	1.50	0.96
F	11		34.2			3.00	1.35	0.43
F	11		30.7			3.00	1.40	0.77
F	13		54.9			3.35	1.55	0.58
F	12		33.4–35.4	6	250	2.04	1.06	0.59
					500	2.78	1.17	0.67
					750	3.36	1.30	0.52
					1000	3.73	1.68	0.66
					1500	4.58	2.68	0.89
					1000	3.58	2.21	0.71
					750	3.13	2.08	0.55
F	5	2	20.2–22.1	6	500	2.69	1.22	0.45
					250	1.60	0.76	0.63
					500*	2.11*	0.85*	0.71*
					1500	3.85	1.55	1.73
					1000*	2.94*	1.32*	1.09*
					750	2.61	1.21	0.89
					500	2.28	1.02	0.67
F	4	2	17–18.6	6	250	1.52	0.60	0.40
					500	2.08	0.95	0.50
					750	2.68	1.24	0.63
					1000	3.09	1.67	0.83
					1500*	3.98*	1.75*	1.61*
					1000	2.76	1.33	0.80
					750*	2.48*	1.17*	0.56*
					500	1.98	1.20	0.46

* Daily averages from three-day periods.

TABLE 27.—EXCRETION OF P_2O_5 IN OLDER CHILDREN

Author	P_2O_5, grams each day	Remarks
Camerer[37]	0.70	Three-year-old boys. Mixed diet
Schabad[324]	1.70	Four year old. Milk and bread
Soetbeer	1.70	Six year ("Phosphaturia"). Mixed diet
Herbst	1.65	About six and one-half years
	1.71	Seven and one-half years. Mixed diet
	1.61	Eight year
Vozarik	1.10	Nine-to 10-year-old boys (4). Vegetarian diet
	1.34	Mixed diet
	1.75	Meat diet
Herbst	1.41	Eleven years, not well developed
	2.05	About 13½ years. Mixed diet
	1.47	Fourteen years, not well developed
Camerer	1.80	Fourteen to 19 years. Mixed diet
Jundell	1.18	Five and one-half-year boy, average daily intake of phosphorus about 2.65 gm.
	1.48	Seven and three-fourths-year-old boy, average daily intake of phosphorus about 3.14 gm.

The administration of hydrochloric acid and ammonium chlorid increases the phosphoric acid in the urine, while sodium bicarbonate decreases it.[122, 257]

Attention should be directed to the importance which has been assigned by recent investigators to phosphoric acid in connection with muscular activity.

Calcium.—The calcium content of the adult's urine is given from 0.16 to 0.37 gm. a day, in terms of calcium oxide. It diminishes gradually in hunger.[69] In the case of Gamble, Ross and Tisdall,[123] an eight-year-old girl, the calcium excretion in the urine during a 15 day fast, while diminishing from the second three-day period, remained fairly high. It dropped from about 0.21 to 0.12 gm. calcium oxid. The excretion of calcium in the urine is dependent on many factors. Conditions which influence the absorption of calcium, its fate in the intermediary metabolism, the combination it forms and its excretion through the intestinal wall must influence the excretion in the urine to a certain extent, no matter how small the amounts of calcium usually are, which leave the organism through the kidneys. Much the greater part of calcium is usually found in the feces. To

TABLE 28.—CALCIUM OXID EXCRETED IN THE URINE (ORGLER[284])

Author	Child	Age	Food	Calcium oxid	
				Daily intake, milligrams	Daily output, milligrams
Birk	I	Newborn	Colostrum	72	4
	III	Newborn	Breast milk	62	4
	I a	Newborn	One-half milk, one-half water, lactose	146	6
	I b	6 days	One-half milk, one-half water, lactose	245	14
	II a	Newborn	One-half milk, one-half water, lactose	113	12
Michel	I	5 days	Breast milk	252	12
	II	11 days	Breast milk	301	15
	III	5 days	Breast milk	232	7
	IV	7 days	Breast milk	296	8
Schlossmann	Kubitz	1 month	Breast milk	332	51
	Kriesch	1.75 months	Breast milk	423	20?
Tobler and Noll	Kurt K	2.5 months	Breast milk	239	37
Michel-Perret	.....	2.5 months	Breast milk	377	3
Schabad[325]	G	3.75 months	Breast milk	364	17
Blauberg	Metzke	5 months	Breast milk	272	31
Orgler	Herbert G	2.5 months	One-half milk, one-half flour soup, sugar	702	23
Cronheim and Müller[76]	II	4 months	Three-fourths milk, lactose	1351	16
	Lo*	4 months	Two-thirds milk, lactose	911	21
Arndt	Carl G	5.5 months	Malt soup	611	18
Orgler	Max G	5.5 months	Two-thirds milk, one-third flour soup, sugar	1230	15
Rothberg	Halm	5.5 months	Skim milk	1373	20
Blauberg	Müller	6 months	Whole milk	2084	17
Birk	St	6 months	One-half milk, one-half flour soup, malt	725	43
Cronheim and Müller	I	6 months	Three-fourths milk, lactose	1273	10
	Hu*	6 months	Whole milk	1512	16

Klotz	G H. W.	6 months 7 months	One-half milk, one-half flour soup One-half skim milk, one-half flour soup, malt	761 770	31 4
Freund[112]	Kramazyk	8 months	One-half milk, one-half flour soup, malt	754	12
L. F. Meyer[250]	B	10 months	Two-thirds milk, one-third cereal decoction, sugar	1394	0
Birk	K	10.5 months	One-half milk, one-half flour soup, malt	866	12
Howland and Stolte	K†	6 months 7 months	Breast milk Breast milk, casein (from cow's milk)	332 341	27 29
Lindberg	L. S. A.	2.5 months	Human milk, average of Period I and II Human milk and human fat	259 224	21 26
Malmberg	Sv. E. O. G.	3.5 months	Breast milk	341 328	29 13
Muhl	B I B II H. V. I. I L. St. I N. J. I	2⅓ months 2.5 months 2⅔ months 3.75 months 5 months	Breast milk Breast milk Breast milk Breast milk Breast milk	309 315 315 297 382	21 26 10 15 20
Hamilton‡	I II III IV	3 weeks–4 months 1 month–5 months 1 month–1.5 months 3 weeks–2.5 months Same	Breast milk Breast milk Breast milk Breast milk Breast milk and calcium chlorid	100–204 134–309 136–179 164–238 279–282	11–7 6–16 5–5 11–9 15–19

* Average of five experimental periods.

† Average of two experimental periods.

‡ The figures represent averages of three to 10 day periods. I, three periods; II, five periods; III, two periods; IV, three and two periods. The infants were born prematurely.

Orgler's[283] table, in which is collected the results of various investigators obtained for the first year of life, some of the newer data are added. The intake of calcium and excretion are given in milligrams of calcium oxid each day (Table 28).

In the athreptic infants of Utheim (27 determinations in 19 infants) the calcium oxid output exceeded 50 mg. in five instances with 83 to 150 mg. The age of these infants varied from 3 weeks to 14 months. During the first two weeks of life the newborn infant excretes from 4 to 15 mg. of calcium oxid in 24 hours. Infants from 1 to 10 months of age excrete from 0 to 51 mg. No difference seems to exist between breast and artificially fed infants. This is borne out by the observations of Chi-Che Wang, Witt and Felcher, on changing feedings in the same infant. Variation in the fat content of the human milk exercised neither a striking nor a uniform influence on the calcium excretion in the urine of the infants examined by Muhl and by Lindberg.

In one of the cases of Malmberg the calcium content of the urine rose during fever from 29 to 37 mg. On the addition of hydrochloric acid to its milk mixture the seven months old infant observed by Shohl and Sato, raised its urinary output from 24 to 31 mg. calcium oxid, while in the case of a nine months infant it decreased from 36 to 29 mg. on addition of sodium bicarbonate. The three boys, 11 to 13 years of age, observed by Baumgardt eliminated, on alkaline food, an average of from 88 to 180 mg. a day, while on acid food, in spite of a greater intake of calcium, the urine contained from 58 to 81 mg., but part of the acid was given in the form of phosphoric acid. In the experiments of Shohl and Sato the organism retained less calcium after acid and alkali administration, while in the experiments of Baumgardt on the acid diet, more calcium was retained than in the control period.

A relationship exists between calcium excretion in feces and in urine so that for instance an increase in the fecal calcium may lead to its disappearance from the urine. Conditions in which the calcium metabolism is altered markedly, as in rachitis and tetany, need not manifest themselves by an increased calcium content of the urine, indeed this may be rather low.

Rüdel gives the excretion of a few children three-fourths to three and three-fourths years of age, as from 34 to 84 mg.; the excretion of two older children aged 13½ to 15 years, falls within these limits. Three children observed by Schabad,[325] aged four years, two months, and five years, excreted 33.4, 61.2 and 68.6 mg. They received a diet of milk and bread with an intake of 2.1, 2.1 and 2.9 gm. calcium oxid. Of the cases reported by Herbst the three children regarded as normal, aged 7½, 8, and 13½ years, excreted on an average 77, 39 and 130 mg. calcium oxid a day, three others, aged 6½, 11½, and 14 years, excreted 262, 151 and 189 mg. The first of these was a delicate boy, whose calcium excretion in the feces was markedly diminished compared with the others, the second and third were underdeveloped children

and the third had also a neuropathic taint. The second voided a turbid urine. Herbst reports further observations on two boys aged about 14 years. These observations are of special interest for the reason that the first boy was growing slowly, the other rapidly. The amounts are the daily averages of six-day periods. One set was obtained from a period in which the boys took long walks, the other from a period in which no special exercise was taken. During both periods the first boy excreted about 250 mg. calcium oxid, the second excreted 121 mg. during the marching period and 215 mg. during the other period. With the relatively lower excretion in the latter case the excretion in the feces was also decidedly less. All the children observed by Herbst were on a liberal mixed diet. The urinary calcium of three boys observed by Baumgardt, aged from 11 to 13 years, the two observed by Jundell, aged five and one-half and seven and three-fourths years, and the four observed by Rost, Herbst and Weitzel, aged from 12 to 13½ years, falls within the limits of 58 to 181 mg. a day. On well controlled diets with three experimental periods of three days each Sherman and Hawley found in 12 children aged about 3½ to 13 years, 17 to 160 mg. calcium oxid as a 24 hour average in the urine, with an intake ranging from about 920 to 1420 mg.

TABLE 29.—EFFECT OF A MILK DIET ON THE EXCRETION OF CALCIUM OXID IN THE URINE (SHERMAN AND HAWLEY)

Period	Milk, cubic centimeter	S. C., aged twelve years, 33.4 to 35.4 kilograms		M. O., aged five years and two months, 20.2 to 22.1 kilograms		K. C., aged four years and two months, 17 to 18.5 kilograms	
		Calcium oxid		Calcium oxid		Calcium oxid	
		Intake, milligrams	Output, milligrams	Intake, milligrams	Output, milligrams	Intake, milligrams	Output, milligrams
1	250	595	31	540	28	540	20
2	500	1040	47	950	25	940	39
3	750	1390	38	1300	33	1310	48
4	1000	1780	133	1690	35	1690	60
5	1500	2510	172	2430	38	2410	50
6	1000	1770	214	1670	34	1650	39
7	750	1420	157	970	33	1320	55
8	50	1040	157	1000	41	930	48

It is demonstrated in Table 29 that an increase of the calcium in the food may be followed by a definite increase in the urine, a fact which does not stand out clearly on comparing the intake and excretion of different individuals. The addition of calcium salts to the food for a protracted period gave results as shown in Table 30.

TABLE 30.—EFFECT OF CALCIUM LACTATE ON THE URINE (ROST, HERBST AND WEITZEL)

Cases	Usual diet		Shortly after daily addition of 3.6 gram calcium lactate		After six months daily addition of 3.6 gram calcium lactate	
	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
A. F.	1550	158	2120	164		
M. W.	1550	72	2120	60	2140	68
A. W.	1550	112	2120	69	2140	48
W. A.	1550	135	2120	208	2140	193

The addition of calcium to the diet in the form of lactate did not exercise a definite, uniform influence on the urinary calcium excretion. In one case, an infant aged 11 months, with signs of rickets and latent tetany a big transitory rise of the urinary calcium occurred in the second three-day period, only after the administration of calcium chlorid.[53] With the administration of calcium lactate there was no very definite increase. With the administration of calcium salt an increased retention may occur, but this does not seem to be long sustained.

It has been claimed that the retention of calcium from vegetables is not as good as that from milk, and furthermore, that a certain amount of milk is necessary to satisfy the demand for calcium in childhood. The experimental basis for this claim is not sufficiently secure.

A group of cases which were formerly described as "phosphaturia" are now called "calcaruria," because the striking feature is an increase of the urinary calcium excretion, and not of the phosphates. Czerny and Keller describe the condition as an anomaly in which for a prolonged period urine is, in most cases, excreted, containing strikingly large amounts of calcium. The reaction of the urine is alkalin, the urine is turbid when voided or shortly afterwards. At times an iridescent film is formed on the surface. The precipitate which separates out is made up of calcium carbonate and calcium phosphate. Soetbeer examined such a condition in a six-year-old girl and at the same time a normal control of the same weight which was kept under exactly the same conditions. The results of two different days given in grams were:

	Total nitrogen, grams	P_2O_5, grams	Calcium oxid, grams
Patient	10.21	1.65	0.382
Control	9.66	1.68	0.113
Patient	11.44	1.69	0.399
Control	10.22	1.73	0.149

For six consecutive days the excretion of phosphoric acid and calcium oxid was:

Day	P_2O_5		Calcium oxid	
	Patient, grams	Control, grams	Patient, grams	Control, grams
1	1.579	1.769	0.400	0.174
2	1.863	1.573	0.457	0.158
3	1.763	2.000	0.394	0.162
4	1.693	1.847	0.465	0.143
5	1.694	1.676	0.411	0.178
6	1.687	1.732	0.382	0.113

There is no doubt that the calcium excretion in the urine of the patient was markedly increased, as seen when compared with that of the control and other normal individuals. The patient excreted less calcium in the feces than did the control. Striking as the comparison is between the urinary calcium of patient and control, the picture would have been more complete if the urine of the patient could have been examined again after the condition had cleared.

An increase of the calcium elimination through the kidneys has been observed in three infants, four to six and one-half months of age, after the subcutaneous administration of magnesium sulphate. These results were reported by Schiff.

Magnesium.—The urine of the adult contains 140 to 290 mg. magnesium in terms of magnesium oxid (Neubauer and Huppert). During prolonged fasting the excretion of magnesium drops (Cathcart. Gamble, Ross and Tisdall[124] from 130 to 131 mg. average of three-day periods). As with calcium, only relatively small amounts of magnesium are excreted in the urine, the bulk leaving the body with the stools. The adjoining table shows the amount of magnesium excreted in the urine during infancy and childhood under various conditions, without laying claim to completeness. It must be added that in some instances, not included, the amount of urine tested did not contain magnesium in sufficient quantity for its determination. On subcutaneous injections of magnesium sulphate the magnesium content of the urine rises markedly, while the excretion in the feces may be increased insignificantly, may remain unchanged, or may even show some decrease.[74,328] Some of the injected magnesium is retained. The administration of calcium salts can increase the urinary magnesium as well as calcium, while the administration of magnesium salts may increase not only the urinary magnesium but also the urinary calcium. The administration of acid did not influence the urinary magnesium of the seven-months-old infant observed by Shohl and Sato, while the administration of alkali diminished the urinary magnesium output of the nine-months-old infant from 38 mg. to 9 mg. magnesium oxid.

TABLE 31.—EXCRETION OF MAGNESIUM IN THE URINE DURING INFANCY AND CHILDHOOD

Author	Age	Food	Magnesium oxid		Remarks
			Intake, milligrams a day	Urine, milligrams a day	
Birk[49]	First five days	Colostrum	19	0.2	
	First four days	Human milk from bottle	9	3	Balance negative
	Second, third and fourth days	Cow's milk mixture	48	4	
	Sixth, seventh and eighth days	Cow's milk mixture	49	10	
	First two and one-half days	Cow's milk mixture	27	7	
	Next two days	Cow's milk mixture	42	4	Balance negative
Blauberg	About 9 weeks	Human milk	47	14	
Howland and Stolte	About 5 months	Human milk	40	6	
	About 6 months	Human milk and casein	58	17	
Cronheim and Müller	4 months	Milk mixtures and 50 gm. carbohydrate	172	39	Averages from eight-day periods
	6 months	Milk, raw and sterilized	159	13	
	4 months	Milk, raw, boiled and sterilized	102	15	Averages of five periods of four days each
	6 months	Milk, raw, boiled and sterilized	169	21	
Birk[47]	4.5 months	Milk, flour soup, malt	131	14	
		Skim milk	107	2	
		Whole milk	101	5	Balance negative
		Skim milk, carbohydrate	72	3	Balance negative
	4 months	Skim milk	98	5	Rachitis and so forth
		Milk, flour soup, malt	112	5	Balance negative
		Whole milk	92	4	Balance negative
	5.5 months	Skim milk	133	6	Well
	9 months	Milk mixture	99	3	Fat, pale, slight rachitis
	10 months	Skim milk	128	6	Slight spasmophilia
		Milk, flour soup, malt	130	22	
Bruck	3 months	Milk, flour soup, malt	160	7	
	8.5 months	Milk, flour soup, malt	104	17	
Blauberg	6 months	Whole milk	150	37	
	3.5 months	Milk mixture	102	47	Atrophic
		Kufeke flour	95	6	Balance negative
Schiff	4 months	Milk mixture	88	15	Atrophic
	6.5 months	Milk, flour decoction, sugar	130	19	Reparation from disorder of nutrition
	6 months	Milk, flour decoction, sugar	89	10	Severe rachitis

Tobler and Noll	2.5 months	Human milk from bottle	28	18	
Lindberg	2.5 months	Human milk from bottle	49	13	Average of two periods
	2.5 months	Human milk and human fat	38	10	Average of two periods
Malmberg	3.5 months	Human milk	73	22	
	3.5 months	Human milk	66	24	
Muhl	2.33 months	Human milk	66	20	
	2.5 months	Human milk	66	22	
	2.67 months	Human milk	73	18	
	3.75 months	Human milk	58	4.7	
	5 months	Human milk	77	15	
Jundell	5.5 years	.....	1310	184	
	7.75 years	.....	1500	185	
Herbst	About 7.5 years	Mixed diet	367	133	Well and active
	About 8 years	Mixed diet	352	35	
	About 13.5 years	Mixed diet	478	43	
	About 6.5 years	Mixed diet	301	19	Not well developed
	11.5 years	Mixed diet	318	35	
	14 years	Mixed diet	414	129	Balance in all cases positive
Rost, Herbst, and Weitzel	13.5 years	Mixed diet	755	122	Average of six-day periods
		Mixed diet and calcium lactate	750	157	
	12 years	Mixed diet	755	194	
		Mixed diet and calcium lactate	750	170	
		Mixed diet and calcium lactate prolonged	666	228	
	13.33 years	Mixed diet	755	165	
		Mixed diet and calcium lactate	750	217	
		Mixed diet and calcium lactate prolonged	666	199	
	13.42 years	Mixed diet	755	175	
		Mixed diet and calcium lactate	750	137	
		Mixed diet and calcium lactate prolonged	666	193	

Sodium and Potassium.—In contradistinction to the alkaline earths, potassium and sodium are normally excreted chiefly by the kidneys. As a rule the amount discharged in the urine is dependent on the intake. For convenience these two alkalis are considered together, without presuming that they can replace one another physiologically. It is only necessary to recall the experiment of Loeb, showing an antagonism of the salts of these elements. Potassium is the sole radio-active element in the organism, and some of its activities have been assigned by Zwaardemaker to this property. In these activities it could be replaced by other radio-active elements in equi-radio-active amounts. But while these claims could not withstand the criticism of Zondek, Hamburger and others, it was found that reduction of potassium below a certain level retards the growth of rats,[261] and that sodium could not substitute for potassium. The data obtained by Cathcart for the fasting adult are of interest. These are given first with those of Gamble, Ross and Tisdall[124] for the eight-year-old child (Table 32).

Table 32.—Excretion of Potassium and Sodium

Milk and egg diet		Fasting			Period*	K_2O, gram	Na_2O, gram
K_2O, gram	Na_2O, gram	Day	K_2O, gram	Na_2O, gram			
3.8	5.4	3	1.596	0.117	1	1.41	0.809
3.8	4.4	6 and 7	1.259	0.202	2	0.8	0.303
		10 and 11	0.806	0.270	3	0.44	0.043
		13 and 14	0.618	0.130	4	0.45	0.080
					5	0.43	0.063

* Average of three-day periods of fasting.

Usually the adult takes a liberal amount of sodium chlorid in his diet, and the sodium exceeds the potassium in the urine. On withdrawal of food, this condition reverses. The infant's food, as a rule, contains more potassium than sodium. The nearest approach to the experiment of Cathcart in the infant seems to be the work of Aron.[22] Three infants, all suffering from tetany, were put on a diet of flour concoction

Table 33.—Potassium and Sodium Excretion in the Urine

	First infant		Second infant			Third infant			
			Day			Day			
	Average of two days	Third day	First	Second	Third	First	Second	Third	Fourth
K_2O, milligram a day	266	249	327	278	194	243	282	195	168
Na_2O, milligram a day	126	49	328	195	165	78	83	271	273

containing from about 16 to 80 mg. nitrogen and from 15 to 82 mg. ash. There was no preliminary period. The infants were aged 17 weeks, seven and 10 months, and weighed about 5.5, 6.7, and 5 kg. (Table 33).

The condition prevailing on the first day in the first infant, with hardly any difference between the potassium and sodium excretion in the urine may be referable to preceding events. But the excess of sodium over potassium on the third and fourth day excreted by the third infant is surprising. In any event it is questionable whether results obtained in spasmophilic infants can be accepted as representative, because in spasmophilia the mineral metabolism cannot be regarded as normal. The elimination of potassium and sodium in the urine of the normal breast fed infant has not been studied extensively.

Potassium and Sodium Excretion in the Urine on a Diet of Colostrum: Daily Average for the First Five Days of Life (Birk)

	First infant		Second infant*	
	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
K_2O	158	42	33	23
Na_2O	112	51	38	14

* The daily average of the second to fourth day of life on feeding human milk from the bottle. In this case the potassium balance was negative.

Daily Average of a Six Day Period of Excretion of Potassium and Sodium of a Nine-weeks-old Baby Fed with Human Milk (Blauberg)

	Intake, milligrams	Urine, milligrams
K_2O	476	227
Na_2O	34	40

This infant observed by Rubner and Huebner for their study of the energy metabolism. It did not gain weight during the period of observation, which may perhaps explain the negative sodium balance.

Lindberg reports results obtained in a two and one-half months old infant fed on human milk (Experiment 1). In Experiment 2 human fat has been added to the milk. Both experiments represent averages each of two three-day periods.

	Experiment 1		Experiment 2	
	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
K_2O	433	239	336	158
Na_2O	146	29	105	13

Five-months-old Baby (Howland and Stolte)

	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
K_2O	533	320	440	322
Na_2O	103	72	131	60

Infants Aged Two and One-half to Three and Three-fourths Months on Human Milk (Malmberg and Muhl)

	Malmberg				Muhl					
	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
K_2O	572	378	584	376	473	341	489	352	497	233
Na_2O	198	71	126	23	156	92	189	109	145	30

Two Newborn Infants Fed on Cow's Milk Mixtures, One-half Milk, One-half Water and 5 Per Cent. Lactose (Birk)

	First infant				Second infant	
	Second, third and fourth days		Sixth, seventh and eighth days		Fourth and fifth days	
	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
K_2O	98	45	237	68	245	64
Na_2O	263	38	238	78	247	48

A few examples taken from results obtained with bottle-fed infants may be given, and a few with older children on mixed diets (Table 34).

In some cases the balances were negative. These have been underscored. It seems that salts may sometimes be stored to be released again for no definite cause recognizable as yet.

In cases of diarrhea, more potassium and sodium may be excreted in the stools than in the urine. In cases of severe diarrhea, as in alimentary intoxication, the excretion of the alkalis in the urine may thus be markedly diminished.

TABLE 34.—RESULTS IN CASES OF BOTTLE-FED CHILDREN

Author	Age	Weight, kilograms	Diet	K_2O milligrams a day		Na_2O, milligrams a day		Remarks
				Intake	Urine	Intake	Urine	
Meyer and Cohn	1.5 months	4.7	One-half milk, 4 per cent. sugar	833	552	530	553	Two-day periods
	1.5 months	4.7	One-half milk, 4 per cent. sugar	848	480	539	173	
	2.5 months	3.9	One-half milk, 5 per cent. sugar	633	300	623	124	
	3 months	3.6	One-half milk, 4 per cent. sugar	870	714	409	341	Retarded development
Bruck	3 months	3.4	One-half milk, flour soup, malt	694	309	430	199	Four-day periods
Cronheim and Müller[77]	4 months	3.8	Raw, boiled and sterilized milk	1116	826	320	268	Five periods, four days each
	6 months	7.8	.....	1852	1410	630	407	each
Blauberg	7 months	7.6	Whole milk	1575	1127	410	343	Six-day periods
Bruck	8 months	5.6	One-half milk, flour soup, malt	1313	1420	890	635	Three-day periods
Meyer[250]	10 months	9.0	Two-thirds milk, oats, sugar	1961	1441	478	331	Eczema
Herbst	6.5 years	21.0	Mixed diet	2186	2297	2900	2161	Pale, delicate, six-day periods
	7.5 years	22.0	.....	2377	2428	3797	4235	
	8 years	24.0	.....	2402	2154	3556	2820	
	11.5 years	21.0	.....	2158	2416	3213	2307	Underdeveloped
	13.5 years	41.0	.....	3036	2602	5080	3917	
	14 years	27.0	.....	2776	2625	4349	3044	Underdeveloped, neurotic
Jundell	5.5 years	18.4	.....	2590	2134	6360	1913	
	7.75 years	23.1	.....	3140	2449	5170	2378	

Steinitz[371] studied the effect of a change of diet from one poor in fat, about 1 per cent., to one rich in fat, about 5 per cent. (Table 35).

TABLE 35.—SUMMARY OF RESULTS CALCULATED FOR POTASSIUM AND SODIUM OXID

	First child				Second child			
	Poor in fat		Rich in fat		Poor in fat		Rich in fat	
	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams	Intake, milligrams	Urine, milligrams
K_2O	1152	815	1135	464	951	728	829	306
Na_2O	471	338	414	241	401	600	371	140
	Third child				Fourth child			
K_2O	937	278	760	97		390		283
Na_2O	385	15	340	12		82		10

The first child excreted, on the diet poor in fat, more potassium and sodium in the urine than in the feces, the balance for both was positive, during the cream period the excretion in the urine diminished, that in the stools rose so high that the balance became negative. The third child also went from a positive to a negative balance on cream, but the second child had a negative balance in both periods and more so on the diet poor in fat, when the excretion in the urine was very high. None of the children was normal. It seems that on a diet rich in fat the excretion of alkali in the urine may drop and this was accompanied by an increase in ammonia.

The results of Meyer[250] on the change from a liberal to an insufficient diet are of interest. An infant aged ten months, weighing 9 kg. during a preliminary Period 1, received 100 calories for each kilogram of body weight, this was reduced to 50 calories for each kilogram. During the first part of this time, Period 2, the baby lost 530 gm., then the weight curve straightened, Period 3, so that in the next period, also of four days' duration, the loss was only 10 gm. The baby was somewhat flabby and had eczema.

	Period 1		Period 2		Period 3	
	Intake, milligrams a day	Urine, milligrams a day	Intake, milligrams a day	Urine, milligrams a day	Intake, milligrams a day	Urine, milligrams a day
K_2O	1961	1441	709	859	679	541
Na_2O	478	331	201	450	186	160

The nitrogen balance was negative on the first three days of Period 1. In Period 2 the potassium and sodium balance were negative, and in Period 3 that of potassium became positive.

In another case, an infant aged three months, weighing 5.8 kg., no analyses were made in the preliminary period. The diet was reduced to 44 calories for each kilogram. During Period 1, lasting three days, the weight dropped 180 gm., during Period 2, covering an equal length of time it dropped 40 gm.

	Period 1		Period 2	
	Intake, milligrams a day	Urine, milligrams a day	Intake, milligrams a day	Urine, milligrams a day
K_2O	839	509	578	418
Na_2O	90	106	126	121

The nitrogen balance was negative for the first four days. The sodium balance was negative in Period 1.

The results are sufficient to show the tenacity with which the organism of the infant tries to guard itself against the loss of important substances.

In the seven-months-old infant to whose diet of simple milk mixture Shohl and Sato added hydrochloric acid, the sodium excretion in the urine rose from 400 to 641 mg., on an average for 24 hours on an equal intake of 570 mg., while the potassium excretion differed but little, rising from 950 to 984 mg. on an intake of 1430 mg. On administration of sodium bicarbonate to the nine-months-old infant the sodium excretion in the urine rose considerably, while on an intake of 947 mg. potassium, its excretion in the urine rose from 578 to 666 mg. The excretion of potassium and sodium in the feces in either case was not so very much influenced.

The excretion of different mineral constitutents has been studied in connection with various disorders of nutrition. In cases of athrepsia Utheim determined the excretion of sodium and potassium as well as of calcium and chlorin. A discussion of all these contributions would lead here too far.

Chlorin.—Like potassium and sodium, chlorin is chiefly excreted in the urine, and its amount in the urine reflects usually its quantity in the food. In hunger the organism gives off its own chlorin (Table 36).

The sodium excreted at the same time was never sufficient to combine with all of the chlorin. Some chlorin is no doubt excreted in other form than sodium chlorid.

TABLE 36.—CHLORINE EXCRETION (CATHCART, AND GAMBLE, ROSS AND TISDALL) [124]

Milk and egg diet	Fasting		Period	Chlorin, grams
Chlorin, grams	Day	Chlorin, grams		
7.8	1	3.2	I	0.53
6.7	3	1.5	II	0.273
	6 and 7	0.92	III	0.202
	10 and 11	0.95	IV	0.089
	12	0.08	V	0.050
	13 and 14	0.25		

On a food poor in chlorin, the chlorine excretion diminishes, nevertheless the balance may become negative, the body giving off chlorin.[81] The experiments of Aron,[22] mentioned above, extended also to chlorin.

CHLORINE EXCRETION ON A DIET NOT FAR FROM FASTING

	Average of two days	Third day	Day			Day			
			First	Second	Third	First	Second	Third	Fourth
Chlorine, milligram a day	89	69	172	65	70	61	98	86	71

These are rather high values, taking into consideration that the breast fed infant of Blauberg excreted, on a daily intake of 203 mg., 13 mg. chlorin. Tobler and Noll register an average daily intake of 69 mg. with an excretion of 59 mg. In the case of Lindberg the average intake was 165 and 124 mg. daily with a corresponding output of 96 and 52 mg. chlorin in the urine. Malmberg's reports on an intake of 267 and 251 mg. chlorin an urinary output of 203 and 177 mg. for twenty-four hours, and Muhl on an intake of 271, 254 and 239 mg., an output of 225, 181 and 166 mg. The case of Howland and Stolte on an intake of 267 and 258 mg., excreted 170 mg.*

Due to the larger amount of chlorin in the food, the artificially fed infant excretes more chlorin in the urine than the breast-fed infant. For instance one of the children aged one and one-half months, examined by Meyer and Cohn excreted 411 and 252 mg. chlorin on an intake of 450 and 457 mg. The infant aged ten months observed by Meyer[250] excreted 748 mg. on an intake of 1123 mg. On an intake of 394 mg.

* The low concentration of chlorids in breast-fed infants' urine permits, on the addition of silver nitrate, a blackening of the solution on standing or heating (5 c.c. urine and 15 to 20 drops of 2 per cent. silver nitrate). This is the so-called Engel-Turnau reaction.[286]

chlorin the infant aged seven months examined by Blauberg excreted 665 mg., and one of the Meyer and Cohn infants two and one-half months of age excreted 64 mg. on an intake of 445 mg. The excretion of chlorin, it is evident, may be rather erratic and for no patent reasons. Sometimes the excretion in the urine may be small, at other times it may exceed the intake. This may occur very readily in cases of disordered nutrition. In cases of diarrhea the chlorine content of the stool may out-balance that of the urine. Keller[186] showed that on a diet deficient in chlorin such as a one-sided carbohydrate diet, only traces of chlorin may be found in the urine of infants. On the addition of sodium chlorid to such a diet some time elapses before larger amounts of chlorin appear in the urine. On the addition of sodium bicarbonate to the diet of an infant aged nine months Shohl and Sato noted an increase of the urinary chlorine output from 454 to 528 mg. on an intake of 545 mg. On the addition of hydrochloric acid to the diet of an infant aged seven months, the chlorin content of the urine increased very considerably, but that of the feces increased relatively even more. The administration of monasodium phosphate by mouth to older children, Röckemann claims leads to a diminution of the urinary chlorin associated with a retention. In acute fevers, particularly in pneumonia, the excretion of chlorin in the urine falls very low, while at the same time the chlorin concentration of the blood is decreased.* [228, 241]

With the cessation of the disease the chlorine output of the urine rises more than can be accounted for by the increased intake of food. In acute fevers, therefore, chlorin is stored in the body. Malmberg vaccinated infants fed on human milk and studied the mineral metabolism before, during, and after the fever, as well as during fever following typhoid vaccine injections. Before and during the initial fever period of vaccination the sodium and chlorine excretion increased only in the urine. During fever, sodium, potassium, chlorine and phosphoric acid elimination in the urine was increased, while calcium and magnesium excretion increased in the feces. The retention of minerals was decreased.

The influence of the administration of certain salts on the excretion of other salts is of utmost interest. A few examples have been pointed out. Bunge called attention to the fact that the introduction of potassium salts into the organism leads to a depletion of sodium chlorid. Meyer and Cohn added sodium chlorid, potassium bicarbonate, calcium acetate and calcium chlorid to the food of infants. Without entering into a detailed discussion of these experiments it was found that the addition of sodium chloride besides causing an increase in the elimination of sodium and chlorin also increased the urinary potassium. The introduction of potassium bicarbonate increased besides the potassium the sodium output. Calcium acetate increased the urinary

* It has been customary to express the chlorine excretion in terms of sodium chlorid. There is no objection to this as long as it is realized that the chlorin of the urine is not solely excreted in the form of sodium chlorid.

sodium, and calcium chlorid the sodium and potassium. A great part of the calcium was retained, while the chlorine balance became negative, showing that the constituents of a salt can part company in the organism, a fact strikingly confirmed by Gamble, Ross and Tisdall[124] with regard to sodium chlorid; a salt formed by the union of a strong alkali with a strong mineral acid. Under the conditions of their experiment, on administration of sodium chlorid more chlorin appeared in the urine than corresponded to the total amount of fixed base. Thus it is explained that the administration of salts like calcium chlorid by fixation of the calcium can act as if hydrochloric acid had been administered, and similar results are obtained on the administration of ammonium chlorid.[28,123,145,365] The administration of calcium chlorid can produce a diuresis, with increased elimination of sodium, and to a less extent, of potassium. The urinary excretion of magnesium and calcium may also be increased. Calcium chlorid has been used to reduce edema.[52,185, 308, 342]

Whether iodin can occur in the urine normally, is not known, neither has the presence of fluorin been determined; both elements are normal constituents of the organisms.

Iron.—Excretion of iron in the urine of infants does occur. Czerny and Keller reproduce a table of Langstein and Edelstein. The urine of an infant aged twelve weeks, weighing 4.6 to 4.9 kg., was collected for 12 days. The food was human milk. The urine contained 0.63 mg. iron. In another infant aged eight weeks, weighing 4.7 to 5 kg., also fed with human milk from the bottle, the urine of 12 days contained 0.19 mg. iron. In smaller amounts of urine, iron may be found in traces. In the urine of premature infants one to four months of age, fed with human milk Lichtenstein found traces to 0.09 mg. iron with a negative balance. Iron is excreted mainly by the feces. Krasnogorski found from 0.08 to 0.55 mg. iron in the urine of several infants fed with goat's milk and with human milk. More iron was retained on a diet of human milk.

There is no available data with regard to the excretion of copper in the urine of infants and children. Since this metal is prevalent in food it should be present in the urine rather frequently. Zinc, tin and perhaps arsenic should also be found at times.

Nitrates and Nitrites.—Mayerhofer reports the presence of nitrates in the urine of breast fed infants suffering from intestinal disturbances. The urine of normal breast fed infants does not contain nitrates or nitrites. The urine of infants losing body protein on a tea diet also gave a nitrate reaction. The presence of nitrates in the urine of the adult is usually referred to their introduction with the food. But there are cases of enterogenous cyanosis, in which the cyanosis is due to methemoglobin formation. The methemoglobin formation is due to the resorption of nitrites from the intestinal canal where they are supposed to be produced from amino groups of protein molecule.[402] The formation of the nitrites or nitrates in the cases of Mayerhofer[243] may also take place in the intestines, as he supposes. The results of

Kastle and Elvove are of great interest. It was found that the organism of higher animals (rabbits) could partially oxidize nitrites to nitrates, and partially reduce nitrates to nitrites, the products being excreted in the urine.

Silicic Acid.—Silicates may occur in the urine of the adult,[132] and their presence may be expected at least in the urine of older children.

Before dismissing the subject of the inorganic constituents of the urine it may be of advantage to indicate, if only very briefly, some of their main functions in the normal organism. They enter into the composition of various structures. They form part of the protein molecule and of some lipoids. They are essential for catalytic activities, for the acid base equilibrium, and the distribution of water. They influence solubility, the permeability of cells and tissues, and their irritability. They are intimately associated with colloidal chemical reactions. They serve for the production of differences in electrical potential, that is, for the production of electrical stimuli, and they play a part in electrical conductivity.

Enzymes.—The enzymes of the urine are regarded by Mayerhofer[244] as probably excretory products, the appearance of which in the urine depends on (1) the slight or marked production of enzymes, (2) the enzyme content of the blood, and (3) the permeability of the kidneys. Furthermore the permeability of the intestinal wall for enzymes must also be taken into consideration. Wherever enzymes are concerned it must be remembered that they are substances solely recognizable by their activity, and that this activity is readily influenced by the environment in which it is displayed. Aside from the influence of the hydrogen-ion concentration that of more or less specific accelerators and inhibitors and their possible interaction cannot be neglected. The neglect of these factors deprives a number of investigations in this field of much of their value. Euler and Svanberg, for instance demonstrated that normal and pathologic urine may inhibit markedly the action of invertase, catalase and diastase.

From birth the urine of infants possesses proteclytic activity which it unfolds in acid solution. This enzyme, therefore, may be regarded as a pepsin.[57] Pechstein asserts that this enzyme is present as proenzyme and in company with the proenzyme of rennin. According to Benfey a trypsin-like enzyme may sometimes occur, or rather an enzyme attacking casein in alkaline solution. Steinitz[372] speaks of the presence of diastase and maltase, which are supposed to be increased in amount in disorders of nutrition.

The diastatic activity of urine was studied by Mayer and McClure and Chancellor. The diastatic activity is rarely missed from birth on. There is no reason why enzymes which have been found in the urine of adults, as for instance erepsin,[99] should not occur in the urine of children. And under certain conditions it is very probable that peptolytic enzymes will be found, such as Pfeiffer[290] found when testing the urine of protein decomposition toxicoses (burns, and so forth)

with glycyl tryptophane. In the urine of a healthy infant aged six months, György and Stenström report the occurrence of urease, the proof not being absolutely complete in the opinion of Lublin. A glycolytic ferment was encountered by Tezner in the urine of a girl aged 10 years with a transitory chyluria. A properly conducted search may perhaps show, under various conditions, the presence of enzymes other than those mentioned. The complexity of a milieu-like urine and particularly urine secreted under pathologic conditions, makes it difficult to understand the significance of its enzymatic activity. Particularly must care be exercised when speaking about variations in the amount of enzyme.

Vitamines.—The examination of urine for so-called vitamines, or, better, accessory food elements, during infancy and childhood should yield interesting results. Muchenfuss treated polyneuritic pigeons with Fuller's earth activated through contact with human urine. The animals improved greatly. Funk and Dubin and Curatolo could confirm these results. Vitamine A could be demonstrated in urine after the intake of food rich in it.[73] The presence of vitamines in the urine of breast fed infants has been demonstrated by Lichtenstein and Euler. It concerns the D group of Funk, and was measured by the influence on yeast fermentation of glucose.

Toxicity.—Quite a number of investigations concerning urinary toxicity have been reported, particularly in the French literature. Many of these express the toxicity of the urine in terms of the urotoxic coefficient of Bouchard. This urotoxic coefficient is calculated from the weight of the animal (rabbit, dog, cat, and so forth) which receives the intravenous injection, the amount of urine required to kill the animal on continuous intravenous injection and the amount of urine for each kilogram of body weight voided in twenty-four hours by the individual whose urotoxic coefficient is to be determined. The living tissue in kilogram killed by the amount of urine voided for each kilograms, is the urotoxic coefficient.* The average normal urotoxic coefficient is given by Bouchard as 0.465.

This method of experimentation has been severly criticized by van den Bergh,[389] who lays entirely too great stress on the importance, of the osmotic conditions. Nevertheless the objections to the method are sufficient, without this, to make conclusions reached in this manner of very doubtful value.

Pfeiffer[289] and Pfeiffer and Albrecht introduced a unit of toxicity based on the drop of temperature caused by intraperitoneal injections of urine in guinea pigs of about 350 gm. These animals received 2 c.c. urine and the rectal temperature was measured every one-fourth hour until the initial temperature was regained. The equation is $T = \frac{t \times Z}{2}$. (T = toxicity of urine for each cubic centimeter. t = the

* Suppose a rabbit weighing 1500 gm. is killed by 80 c.c. urine. The individual in question weighs 60 kg. and voided 1800 c.c., that is, 30 c.c. for each kilogram a day. This 30 c.c. is sufficient to kill a rabbit weighing 562 gm. (or any other animal) and the urotoxic coefficient is, therefore, 0.562.

lowering of temperature in 0.1 of degree Centigrade. Z = time from injection until the initial temperature is reached in minutes.) The total toxicity is the toxicity of 1 c.c. multiplied by the number of cubic centimeters of urine voided in twenty-four hours. The toxicity of normal urine for each cubic centimeter rarely exceeds 300. This toxicity is increased in various diseases.

Efforts at isolation of toxic substances were not wanting. Griffiths isolated various substances from the urine in various cases of infectious disease, using a method previously described by Luff. But his results do not inspire much confidence. With the same method Albu obtained toxic material from some of the febrile patients he examined. Abelous and Bardier speak of the presence and significance of pressor and depressor bases in urine. The results of Abelous could not be confirmed by Granger. Bain isolated from urine a pressor substance which is, in all probability, isoamylamine.

It is evident that one can obtain from urine toxic substances in various ways, taking into consideration for instance the toxicity of potassium salts. If substances contained in urinary distillates, as for instance the previously mentioned urinod, or phenols, prove toxic this does not mean that the urinary toxicity, such as seen with injections of urine, is due to these substances, as they occur in the native urine. In former years great stress has been laid on the part potassium salts play in the urinary toxicity. The experiments of Amberg and Helmholz[12] with regard to the influence of sodium salts on the toxicity of potassium salts on intravenous injections in guinea pigs, show clearly that the interpretation of results obtained with complicated mixtures demands great caution.

TABLE 37.—INTRAVENOUS INJECTION OF URINE IN GUINEA PIGS (ARONSON AND SOMMERFELD)

	Cases	Result of experiment	
		Animal died	Animal survived
Normal	18	..	18
Measles (absolutely sure of 38)	44	33	11
Scarlet fever	20	1	19
Diphtheria	3	..	3
Serum exanthem	3	3	
Chicken pox	16	10	6
Vaccinated	14	5	9
Doubtful exanthem (fourth disease)	2	2	
Miscellaneous	26	4	22

In the pediatric literature a statement of Gundobin is often quoted, that the urine of the newborn is more toxic than that of the infant and adult. The urine of the third and fourth day is particularly toxic. The statement is based on the work of Kotscharovsky and Glein, both of whom reported their findings in Russian. Uffenheimer[385] did not find a marked toxicity of the urine from two newborn infants, while that of a third was quite toxic for guinea pigs. Aronson and Sommerfeld used the intravenous injection of 2 c.c. urine in guinea pigs weighing from 180 to 220 gm. (Table 37).

In the condition in which the problem of urinary toxicity finds itself it is obvious that not too much significance can be attached to such observations.

Wildbolz Reaction.—The urine of actively tuberculous patients contains, according to Wildbolz, a specific antigenic substance, which on intracutaneous injection of the properly prepared urine gives rise to a reaction similar to the tuberculin reaction in patients sensitive to tuberculin. This may be the patient who passed the urine. A number of investigators tried this reaction in children.[9,19,91,195,199,235,331] The specificity of the reaction has been contested, or if acknowledged, its value for the differentiation of active tuberculosis has been accepted only rarely.

Morphologic Elements.—According to Hamill and Blackfan the occasional presence of hyaline casts and cylindroids in the urine of children has no further significance. Small numbers of epithelial cells, and a few leukocytes may also occur normally. Lust[219] sees in the occurrence of epithelial cells in larger numbers in the urine of male infants a symptom of exudative diathesis, an opinion in which Beck concurs. The appearance of larger numbers of leukocytes, of various casts, red blood corpuscles, and so forth, will receive attention in the chapters dealing with the diseases of the urinary tract. Certain forms of hematuria claim attention here. A rare cause may be telangiectasis of a renal papillæ, such as cited by Eschner in which the intermittent unilateral hematuria started when the patient was thirteen years old. The occurrence of red blood corpuscles in the urine has been noted in the course of various infections. It can occur after exercise.[271] In urine of weak infants and children, when attacked by some infection such as pyelitis, or grippe, or on vaccination, a few red blood corpuscles may be found. Castro calls this phenomenon "erythrocyturia minima." It may persist for months. While it may occur in connection with pyelitis, it may happen without evidence of any infection or other lesion of the urinary tract. The portal of entrance of the red blood corpuscles is the kidney.

From the point of view of differential diagnosis Castro puts in first place the forme fruste of scorbutus, recalling a very interesting case of Lust[220] in which a pronounced hematuria lasting three weeks in an 11 months old baby, without other signs of scurvy yielded to antiscorbutic treatment within five days.

A nearly uninterrupted hematuria without evidence of any lesions has been seen. It is very rare. Aitken reports it as congenital, hereditary and familial hematuria. Of 17 members of a family, 10 were afflicted and it was found several times within the first weeks of life. . . .

During the first days of life the urine contains urates; later, under conditions not different from those in adults, urates, phosphates, and oxalates may be seen in crystalline form.

The presence of antistrophic lipoid substances has been noted in the urine of children by Reinike. As a rule their appearance is laid to degenerative processes in the kidney, but Genck thinks that the injured kidney allows these lipoids to pass through from the blood. A small number of cases of nonparasitic chyluria in children have been reported; Goebel[129] collected from the literature 73 cases of this type of chyluria and of these seven occurred in children. In one instance two other members of the family were affected. The chyluria is frequently transitory, sometimes lasting only one day. As a rule the prognosis is good, but in the eight-year-old girl reported by Hymanson the chyluria was associated with a fatal chronic diffuse nephritis. In this case lecithin and cholesterin were found. It is claimed that cholesterin occurs in normal urine in traces.[139] The chyluric urine contains cellular elements, albumin, frequently sugar and fat globules. These may be derived from the fat of the food as demonstrated, for instance, by Tezner.

Infections of the urinary tract give rise to the presence of bacteria in the urine. But the urine may contain microorganisms in the absence of demonstrable lesions of the urinary tract. Recent investigations make it very doubtful whether it is possible for bacteria to pass from the blood through an uninjured kidney into the urine (Helmholz). It is well known that typhoid bacilli pass into the urine in typhoid fever, and the presence of diphtheria bacilli could also be shown in the urine of diphtheritic patients.[110] In certain cases of scarlet fever, small pleomorphic microorganisms were isolated from the urine by Dick and Henry.

In the course of extra-urinary infections various microorganisms may be found in the urine of infants and children. Beeler and Helmholz obtained positive cultures from the urine of 12 of 18 children less than two years of age. In the urine of older children microorganisms were found more rarely. Gram positive cocci preponderated. Schwartz[345] found gram negative bacilli in 38 of 63 infants suffering with gastro-intestinal disorders. In about 20 per cent. of the positive cases the number of microorganisms was sufficiently large to consider it a bacilluria. The incidence of bacilluria, as well as of the occurrence of bacteria, was considerably greater in girls than in boys. Bacteria, preponderantly gram positive cocci, were found in the urine of normal children by Beeler and Helmholz in five of 12 children under two years of age. Only four specimens of urine from 18 girls over two years of age gave positive cultures. Soldin and Langer report *Streptococcus*

lacticus in the urine of 128 of 138 children without evidence of pyelocystitis. In no case was the urine sterile on repeated examination. Helmholz and Millikin found this coccus in only three of 78 specimens of urine. These infants were not hospital cases but were brought to an infant welfare station for no other reason than supervision, and may be designated as normal. Thirteen infants had some other streptococcus. From 32 specimens of urine staphylococci were obtained, and from two, colon bacilli. The bacteria never occurred in large numbers.

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CHAPTER CIV

DISEASES OF THE BLADDER

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Malformations.—Complete absence of the bladder is exceedingly rare. Cases have been described in which one or both ureters have opened into the rectum, urethra or vagina, or at the umbilicus. Patients have lived for many years without a bladder, the ureters opening into the urethra, forming a reservoir for urine at their lower end by dilatation, a terminal constriction existing at the point of entrance into the urethra, with possibly a certain amount of spasmodic contraction.

Treatment.—Implantation of the ureters into the sigmoid or the construction of a new bladder, as in cases of exstrophy of the bladder, have been resorted to in ameliorating this condition.

Multiple Bladder.—Multiple or divided bladder, with or without a double urethra, is a rarity, although instances of double bladder with double penis, and urethra for each, have been reported. There may be several complete and distinct cavities divided by definite septa Cases have been recorded in which calculi were found in one pocket while the remainder of the bladder appeared healthy. A displaced ureter may open into a dilated pouch or diverticulum of a so-called multiple bladder.

Diverticulum of the Bladder.—This may be *congenital* or *acquired. Congenital diverticulum* may result from obstruction to the urinary flow during embryologic development and a ureter may be so displaced as to open into the sacculation. *Acquired diverticulum* occurs as a result of obstruction to the urinary flow with resulting over-distention of an inflamed bladder. Inflammation of the bladder may naturally and easily occur. All diverticula contain a mucous lining. Congenital diverticula are, as a rule, supposed to be single. Their location may be near the ureteral orifices or upon the lateral or posterior walls of the bladder. However, they may occur in any position. Their size varies from that of a pea to a lemon. There may be complete or incomplete retention of urine. The only satisfactory means of diagnosis is by means of a cystoscopic examination of the bladder or occasionally with cystography.

The appendix may be low in the pelvis and may become attached to the bladder. In abscess formation the abscess may be chiefly in the culdesac of Douglas. Such a case was seen and the abscess was drained from the perineum.

So far as diagnosis is concerned, all the individual factors in the case must be taken into consideration. The treatment depends entirely upon the individual circumstances.

Patent Urachus.—Patent urachus with a cyst-like dilatation or diverticulum at the apex of the bladder may exist; this cavity may communicate with the bladder, forming a cystic tumor or, becoming infected, may form an abscess discharging pus at the umbilicus. Cystoscopy may aid in the diagnosis.

Urachitis.—Occasionally a little concretion is formed in this channel which becomes infected and discharges pus. Again, this entire tract may open into the bladder and urine may be discharged freely.

Diagnosis and Treatment.—The diagnosis and treatment are in accordance with the pathologic anatomy of the condition and the surgical principles involved.

Fistuli of Urachus.—Umbilical fistuli of the urachus are not uncommon and may be suspected where any umbilicus for an unusually long time discharges small quantities of fluid, frequently causing excoriation and maceration of the surrounding skin. The fistulous tract is lined with epithelium and urine exudes. Deformities of the urethra, such as stricture, valvular obstruction, etc., or of the genitalia, frequently co-exist.

Treatment.—Urethral obstruction through strictures or valvular blocking, etc., must receive consideration before undertaking plastic or other operations for treatment of the fistula. If obstruction exists, simultaneous removal of it is essential, as death may result from retention and peritonitis, and under these conditions, even applications of caustics to the fistulous tract may endanger life.

Prolapse of the Bladder (Inversion).—This is exceedingly rare and occurs almost exclusively in females.

Congenital weakness of the neck of the bladder and urethra must be assigned as the predisposing cause, together with the spindle-like shape of the child's bladder, and the funnel-shaped urethra. Exciting causes are usually some straining effort at micturition or defecation, crying, sneezing, etc. Considerable dilatation of the urethra usually occurs together with a relaxation of the internal urethral orifice. A history of incontinence prior to the inversion is usually obtained. After violent straining efforts a pyriform, red, vascular, elastic and soft reducible tumor, the size of a walnut, appears between the labia above the vaginal orifice. The tumor becomes larger and more congested in crying and straining, and the orifices of the ureters may be detected or brought into view by gentle traction, the urine exuding from them.

Diagnosis.—Diagnosis in this condition is important, as it has been mistaken for polypoid tumor and its removal attempted. The diagnosis is based upon the finding of the described protruding mass, which is reducible and usually discharges a quantity of urine during this process (Weinleshuer).

Treatment.—The treatment consists in reducing the protruding mass with attempt to retain the bladder in place by means of a bandage. If this is not successful, narrowing of the urethra by plastic methods must be resorted to.

Exstrophy of the Bladder.—An exstrophy of the bladder may be defined as a congenital absence of its anterior covering wall with deficiencies in the development of the abdominal parietes and pelvic girdle.

The exstrophy may be complete or incomplete. When complete the bladder appears in the hypogastric and prepubian region in

FIG. 182.—Ectopia of the bladder. Epispadias cryptorchism, dislocation of the umbilicus, absence of the symphysis. (*a*) Cicatrix of an operated inguinal hernia, (*b*) umbilicus, (*c*) mouth of the ureters. (Pfaundler and Schlossmann.)

the median line, as an inflamed reddish-colored projecting tumor. This is the mucous membrane of the everted posterior bladder wall. In the lower part the two ureteral orifices may be found, through which the urine escapes. There is a whitish cicatricial zone separating the mucous area from the surrounding healthy skin. The whole surface is usually much excoriated from constant urinary dribbling.

In incomplete exstrophy there may be only an inferior or superior vesical fissure or an ectopic bladder. It is more properly described as a bladder hernia.

The condition was first described by Schenck in the sixteenth century. Bartholin published the first case of bladder exstrophy in 1670.

This condition is usually accompanied by various genito-urinary deformities, one of the commonest being that condition known as "split pelvis." The origin appears clearly to be teratologic and due to failure of development during embryonal life.

In size an exstrophied bladder varies from that of a nut in the infant to the size of an orange in the adult. The external genital organs share in the malformations. In the male there is epispadias and a rudimentary penis. The prostate and dependencies may be absent. The scrotum is normal in form but small and flat. The testicles are usually ectopic. In the female there is a split clitoris, the bladder and malformed urethra opening into the vagina or just above it. The vagina is only a small channel. When the pubes are widely separated some authors describe a dense fibrous band as supplying the deficiency.

Bladder exstrophy is rare and occurs more frequently in male children than in females. Neudörfer's statistics give its frequency as 1 in 50,000 births. The majority of children born with this deformity die early unless operated on.

The most important symptom is the constant incontinence of urine. There is a peculiarity in the gait owing to the separated pubes. Outside of the extremely disagreeable results following the constant urinary dribble, there is no danger to life and such a condition may be borne during a long life. Vigneau in 71 cases found that 10 died between the tenth and twentieth year, 15 between the twentieth and fortieth, and five between the fortieth and fiftieth; one reached the seventieth year. There is always the danger of a kidney infection.

Treatment.—The treatment is either (1) providing for the wearing of an apparatus to gather and hold the urine, or (2) operation. Apparatuses are of many kinds, and their greatest effect is the protection of the skin from the urine. They do not remedy the cause and are most inconvenient and unsatisfactory.

Operative Treatment.—The operative treatment of bladder exstrophy has always been attractive to surgeons. Many methods have been devised. These may be divided roughly into two classes, *viz.*, plastic operations and those with the object of radical cure.

The plastic methods were inaugurated by Roux in 1852. He covered the exposed bladder with skin strips to protect the mucous surface. Variations in this method have been devised by Richard, Le Fort, Billroth, Thiersch, and others. These methods do not obviate the necessity of carrying a portable urinal, the formation of secondary calculi or the danger of an ascending infection.

Attempts to use the rectal sphincter were made by Lerda, Subbotin and Gersung. These procedures generally consisted of tunneling a space between the sphincter ani and rectal mucosa and drawing through it a folded strip of bladder wall as a tube, the anal sphincter closing this new urethra as well as the anus. These methods did not do away with the danger of ascending infection.

Methods of returning the exposed bladder into the rectum and reconstituting the bladder neck with a sphincter by approximation of the separated pubes have been devised by Trendelenburg, Berg, Schlange, and others. In general these have not fulfilled their expectations and the mortality has been high. Besides, the operations are complex.

Simon in 1851 attempted to draw off the urine into the rectum, but his patient died. Maydl in 1894 introduced his celebrated method of double anastomosis of the ureters into the iliac sigmoid. Peters in 1909 implanted the ureters into the rectum extraperitoneally. Makkas in 1910 utilized the cecum as a bladder and the appendix as a urethra. Mayo has very recently reported the results in 37 cases of exstrophy operated on at the Rochester Clinic since 1896. In six plastic methods were used but did not control the flow of urine; in three operation was by the Maydl-Moynihan method; of these three patients two died in the hospital of uremia; 13 patients were operated on by the transplantation method, that is, anastomosis of the ureter into the large intestine and tubularizing the ureteral entrance for about 1¼ in. in the bowel. In these 13 cases there was one operative death. Three died from other diseases within a few years after operation. The remaining patients are all doing well since recovery and are able to attend normally to their occupations.

Orloff collected 56 cases of Maydl's operations. Eleven patients died within 21 days after operation, four from peritonitis. Of the other 45, five died later from ascending infection.

Moynihan successfully performed an extraperitoneal implantation of the exstrophied bladder into the rectum.

Rupture of the Urinary Bladder.—Rupture of the urinary bladder may be intraperitoneal, extraperitoneal or subperitoneal. A rupture of the urethra may co-exist when the base of the bladder is involved in the rupture.

Partial rupture exists when the lesion occurs within the limits of the peritoneal covering, the mucosa and muscularis alone giving way, forming the subperitoneal type of rupture. Partial ruptures involving only the mucosa, muscularis or serosa have been described. Tears in the mucosa only are probably much more common than ordinarily supposed and as the use of the cystoscope becomes more common a larger number of correct diagnoses of these cases will undoubtedly result. Intraperitoneal ruptures are more frequent than extraperitoneal. In the type of rupture most frequently occurring all the coats are torn and the tear is vertical.

Etiology.—The most important predisposing cause is distention of the bladder. The determining causes are most commonly accidents of severe type, the traumatizing agent acting directly upon the bladder with few exceptions. The most prevalent types of accidents are:

1. A hard blow over the region of the bladder, for example: A kick from a horse.
2. Falling from a height.

3. Crushing injuries.

4. Over-distention of bladder before operation or for purpose of diagnosis and treatment.

Rupture of the bladder in children rarely occurs and among collected cases those from traffic accidents seem to predominate. The rarity of this injury in childhood in spite of the many kicks and falls they receive must be because the bladder in children is rarely found greatly distended, as owing to the greater sensibility of the bladder in the young, micturition is more frequent, the tissues are more yielding and elastic, and the sacro-vertebral angle is less prominent than in later life (Stein).

Symptoms.—Shock is present in most cases but usually must be attributed to the severe nature of the trauma. The first symptoms are pain in the abdomen, a feeling of something giving way within, difficulty or inability to walk or even rise (in consequence of fracture of pelvic bones or from shock), an urgent desire but inability to urinate even the smallest quantity, or possibly a few drops mixed with blood may be passed. In the intra-peritoneal rupture all symptoms are much more severe. The shock is greater and the symptoms of peritonitis usually set in within a few hours and increase in severity. The infiltration of urine may be extensive, descending into the perineum, scrotum and thighs, and ascending into the abdomen and back. Anemia is rarely recorded as a pronounced symptom of rupture of the bladder and no case is recorded of death from hemorrhage, as contracture of the muscular walls limits severe bleeding from any wound of the bladder.

Objective Symptoms.—Bladder dulness cannot be outlined but iliac dulness or a diffuse area of dulness may be localized instead. *Per catheter* a small quantity of blood-stained urine may be drawn off or if a catheter has passed through the tear in the bladder a large quantity of fluid (peritoneal exudate and urine) may be obtained. (The presence of an abnormally high percentage of albumin suggests an admixture of peritoneal exudate.)

Diagnosis.—Difficulty or inability to urinate is not a uniform symptom as the patient may have no difficulty in voiding urine and may pass a large quantity. For purposes of diagnosis the symptoms may be divided into (1) those of the first 24 hours, that is, those arising from the bladder, and (2) those after the first day, for example, symptoms of peritonitis; but frequently no such definite lines can be drawn. A tentative diagnosis is possible in most cases after the subsidence of shock and a careful and thoughtful consideration of all bladder symptoms and the history. Pain and tenderness over the hypogastrium are almost conclusive evidence and exploratory operation is at once indicated. The use of a catheter in suspected bladder rupture is *entirely inadvisable* as sterile catheterization cannot be assured and the early onset of peritonitis usually results. Filling the bladder with fluid or air, as has been suggested, may render an incomplete rupture complete and also increases the danger of infection.

Prognosis.—Prognosis depends upon timely therapy. Unquestionably the earlier the diagnosis and the sooner the surgical interference, the more favorable the progosis. In intraperitoneal ruptures the abdomen must be immediately entered and the bladder opened. If the bladder only is opened, the rupture may not readily be found. As the urine in these cases is, as a rule, uninfected, no infection need be expected and the bladder as well as the abdomen may be completely closed and the patient catheterized at regular intervals; however, on account of the difficulty of catheterizing children, there is no objection to keeping a drain in the bladder. This is preferable to the use of a permanent catheter in children.

In extraperitoneal rupture the mode of attack may from necessity be either from below or above or even combined, depending on the location or the drainage necessary. In order to facilitate the healing of these ruptures the bladder must be kept thoroughly emptied.

Circulatory Disturbances of the Bladder.—This is a condition which may occur in children, principally as an active hyperemia. It may be generalized or there may be localized punctate areas attaining the size of a ten-cent piece or larger. Again there may be hemorrhages of the submucosa which may be referred to as purpura. However, at present purpura is considered a general infection and these disorders cannot be considered as strictly of a circulatory type. Passive congestion may occur from pressure on the bladder veins and in both active and passive congestion the mucous membrane may be swollen, thrown into large folds, and appear glossy or even edematous.

Hematuria Vesicalis.—Although, strictly speaking, they are not circulatory disorders, hemorrhages from the bladder have been encountered under various conditions, as in scarlet fever or scurvy. True hemorrhagic conditions may occur following trauma, as from instrumentation or violence, or may be the result of a fall or crushing injuries or foreign bodies. Among the diseases in which hemorrhages from the bladder have been encountered are hemophilia, scurvy, morbus maculosus Werlhoff, typhus fever, hemorrhagic smallpox, septicemia and purpura.

Hernia of the Urinary Bladder.—The urinary bladder in part or in whole may appear through any of the common or uncommon hernial orifices of the lower abdominal wall. It is said to occur in about 1 per cent. of all hernia and to December, 1918, less than 400 cases of all types had been found recorded in the literature of the world (Gay).

The occurrence of bladder hernia is extremely rare in infancy and childhood and of 164 cases of vesical hernia collected from 1896 to 1914 (Heineck), seven cases were between the ages of 18 months and 5 years, six cases between 6 and 14 years, and nine cases between 16 and 25 years. Not one patient is reported to have been operated on during the first year of life. Hernia occurs most frequently in males and most commonly in the inguinal region; in females in the femoral region.

Anatomically they may be hernias of the linea alba, or they may be of the obturator, femoral or inguinal type, and according to their anatomical relations may be divided into direct or indirect, interstitial or intra-parietal, complete or incomplete, pudendal or scrotal. According to the relation the herniated bladder bears to the peritoneum they may be designated extraperitoneal, intraperitoneal or paraperitoneal. They may be single or double and may be reducible or irreducible, inflamed, incarcerated or strangulated. In most instances, in addition to the bladder, the hernial sac contains omentum or intestine. True primary vesical hernias are pathologic curiosities. The para-peritoneal form is not infrequently a sliding hernia and is frequently caused by a constant pull exerted by the sac of an existing hernia upon the peritoneal covering of the urinary bladder.

At first most bladder hernias are unquestionably reducible, later becoming irreducible.

Etiology.—The etiology is largely that of hernias in general, together with any conditions causing prolonged overdistention, overstretching, impaired contractibility, restricted mobility, etc. of the urinary bladder. Important factors in this regard are congenital malformations of bladder walls, diseases of the lower urinary organs impairing the expulsive force of the bladder, or hindering the outflow of urine, such as cystitis, urethral strictures or valvular blocking of the urethra, phimosis, calculus, etc. Abnormal increase of perivesical fatty tissue (lipoma prevesical) plays an important rôle in some cases.

Symptoms.—Pre-operative signs and symptoms may be unmistakable, vague, or entirely lacking. In addition to the symptoms ordinarily present in hernia, vesical hernias present peculiarly suggestive and at times positive signs of their presence. They may be congenital or acquired, recent or recurrent, varying in size, shape and rate of growth as well as in the amount of discomfort and disability entailed. They are frequently associated with or secondary to pelvic, vesical or urethral diseases. The shape may be cylindrical, ovoid or elongated. The hernia is either soft, elastic and fluctuating, or hard and non-elastic. The swelling gives a dull or tympanitic percussion note.

Pain is inconstant and may be entirely absent. The size of the hernia may change rapidly according to the amount of urine in the bladder, the amount of viscus engaged in the extrusion and the position of the body. The most constant indicative sign clinically is a hernial tumor which disappears after micturition. Pressure over the mass causes a desire to urinate or may even cause expulsion of urine.

Subjective urinary disturbances are frequent and painful micturition, and pain at the end of difficult urination. The patient may have to resort to pressure upon the hernial protrusion in order to empty the bladder or he may have to asssume unusual positions in order to void urine.

Objectively there is increased swelling of the hernia with accumulation of urine and decrease with voiding. Injection of fluid or air

may be resorted to to cause increase in the size of the hernia for diagnostic purposes, or a sound introduced into the bladder may be made to enter the herniated process.

Cystoscopic examination may show the opening of the herniated bladder process and distortion of the bladder outline.

Treatment.—All hernias of the bladder, irrespective of age, sex, size or shape, call for operative treatment.

Technique of Operation.—First expose and free the herniated organ or organs and then effect reduction into the abdomino-pelvic cavity. The hernial sac is next taken care of and the weakened hernia area strengthened according to one of the approved methods. Very rarely is resection of the herniated bladder process necessitated. If it is found difficult during the operation to distinguish the true hernial sac from the tumor mass a sound may be introduced into the herniated bladder process as mentioned above. Wounds of the bladder produced during the operation for hernia should be immediately repaired and give good results if proper after-care is carried out. The operative treatment of vesical hernia is highly satisfactory and has practically no mortality.

A case reported by S. G. Gay* is most unusual and interesting: The patient was a negro male child, five years of age, with a strangulated left indirect inguinal hernia. The operation proved the existence of a transposition of the cecum and appendix from right to left, both organs being found in the hernial sac together with a small pouch of the urinary bladder.

Cystitis.—Escherich is given credit for first pointing out in 1894 the frequent occurrence of cystitis in children, especially in girls. Bacillus coli, the most common cause of cystitis in adults, is also by far the predominating causative factor in children. In 60 of Escherich's cases the bacillus coli communis was found present alone or in mixed infection 58 times. The work carried out by his pupils and most later observers bears out the correctness of his original observations, and also has emphasized the importance of bacillus coli cystitis in childhood.

The author, from the few cases he has had under personal observation, does not agree with the general view that a primary cystitis is as common as the pediatrician is inclined to believe; that if cystoscopy, ureteral catheterization, and cultural methods are employed, it will be found that we most frequently deal with a pyelocystitis; and, as described under "Instrumentation of Children," pelvic lavage offers rather startling and satisfactory results.

We admit that there is a great preponderance of so-called cases of cystitis in girls, the access of the bacilli being much easier than in the male. The most common organism is the colon bacillus. In cases of infectious diseases, particularly typhoid fever, I am rather inclined to believe that a bacteriuria first exists and a pyelocystitis

*Amer. Jour. Surg., December, 1918.

easily sets in, so that we do not deal in these cases with a simple typhoid cystitis.

Among other causes of cystitis are the streptococcus, staphylococcus, bacillus pyocyaneus, the bacillus of diphtheria, bacillus mesentericus, tubercle bacillus, gonococcus, and others. Among the contributing causes are vesical calculi, tumors, foreign bodies, rupture of an abscess into the bladder, or an ascending urethral infection, for example, gonorrheal urethritis. The passing of instruments is a frequent source of cystitis. Hematogenous infections of the bladder do occur. Cystitis may develop during the course of typhoid fever or other infectious diseases. Tuberculous cystitis as a primary infection is extremely rare but may be a focal infection in children with tuberculosis elsewhere in the body, especially from other parts of the genitourinary tract, that is, kidneys or testicles.

Symptoms.—Cystitis cannot easily be separated from pyelitis. Clinically one may distinguish between two forms in early childhood: First, those with well-marked general symptoms, such as general malaise, restlessness, fever, pallor, general debility and anorexia, with no sign or symptoms pointing to involvement of the urinary tract. Second, in addition to the more or less marked general symptoms definite indications point to involvement of the urinary tract, such as frequency, pain or difficulty in urination, colicky pains in hypogastrium with tenderness over this region and signs of a urethritis or pain and redness of the meatus. It cannot be too strongly emphasized that a thorough urinalysis should be made in all cases, especially in any which show obscure febrile conditions, or when other general symptoms are prominent and all local manifestations are wanting, as will be the case in a large number of cases of cystitis in infancy. Cystitis not due to the bacillus coli is prone to run a much more severe course and blood is found more frequently in the urine. Pyocyaneus cystitis, which may be a complication of a general pyocyaneus infection, is characterized by hemorrhages in the skin and can be differentiated from the other varieties only by an examination of the urine.

In the acute cases there may be both pain and tenderness in the region of the bladder, besides frequency of urination, tenesmus and pain. The quantity of urine passed may be very small and there may even be dribbling. When the tenesmus and pain are severe prolapse of the rectum often occurs. In many instances there may be practically a complete absence of all local urinary symptoms and in these cases it has been frequently observed that the children cry before the act of urination.

Diagnosis.—If it is possible to employ cystoscopy and ureteral catheterization in diagnosis, methods which should be used more frequently than they are, the differential diagnosis as well as the character of the infection is readily established. It is true that a reflex condition as well as cerebral and spinal diseases may produce bladder symptoms and the cause thereof must be established. The urine, however, in those cases is sterile.

Prognosis.—As regards prognosis, it depends entirely on the cause and the general health of the child, and it can only be said that the course is rather uncertain. Cases in which no pathologic condition exists to allow of easy infection offer the best prognosis. If it is caused by pyelitis relapses readily occur. However, under favorable management recovery occurs. If tumors, stones, foreign bodies or calculi are the cause of the inflammation, the prognosis is good following their removal.

Treatment.—This depends entirely on the cause. If tumors, calculi, or other causes exist which can be corrected by surgery, to secure results, operative interference of necessity must be instituted. In gonorrheal infection the treatment is that advised in the chapter on that subject. The usual treatment which is efficient in pyelitis and pyelocystitis is undoubtedly exceedingly common. Medical treatment consists in the administration of alkalies when the urine is acid and for a short period of time hexamethylenamin is to be given. Whenever there is pain or tenesmus hot applications, hip baths and opiates are indicated. When acute symptoms are absent it is not objectionable to give the bladder local treatment. Argyrol, or preparations of this kind, can be instilled or 1:10,000 silver nitrate solution may be used for irrigation.

Bacteriuria.—Roberts, in 1881, was the first to call attention to a disease which he termed bacteriuria or bacilluria, though later writers have doubted whether this author really observed a case of true bacteriuria, rather inclining to the belief that his was a case of pyelitis or cystitis. Among the earliest reported cases of true bacteriuria are those of Schattelin and Rheinhold, Ultzman, Rosenheim, Melchior, and a few others. It was left to Krazin to more clearly define bacteriuria and establish it as a definite entity. The first case of true bacteriuria was recognized and reported under this name by Clapatt in 1896 (Un cas de bacteriurie chez un enfant. Rev. Mens d. mal de l'enfance, 1896). George Mellin found four other cases reported in the same year and a total of 11 cases up to 1903. The only reason, however, why it is so rarely recognized is because of the lack of definite disorders or symptoms resulting from it and Mellin in 1900 demonstrated this by finding by routine examination of the urine not less than 10 cases within a short period.

Definition.—If freshly voided urine is turbid in the absence of pus, the turbidity being due to the presence of microörganisms, in the absence of a demonstrable lesion inflammatory or otherwise, in the urinary tract, this condition is referred to as bacteriuria. In contradiction to this definition of bacteriuria, as it is still defined in modern textbooks and by practically all the older and many modern writers, I have oftentimes treated cases in which the urine was perfectly clear at the time of observation, which in some instances covered a period of years; yet these cases showing apparently clear urine must be included under the classification of bacteriuria as repeated cultural examinations have shown the same kind of bacteria as constantly present.

Another class of cases exists in which bacteriuria pure and simple is co-existent at some time or other. These are inflammatory conditions of the urinary tract, high or low, or of the adnexa or adjacent organs, and accounts for pus more or less abundant in the urine, in addition to bacteria. While this condition is not at all uncommon in adults, it unquestionably occurs fairly frequently also in children. The practical importance of bacteriuria rests in recognizing the pathogenic bacteria and determining their mode of entrance into the urinary stream.

In the acute infectious diseases, such as typhoid fever, it is not uncommon to find the bacillus typhosus in the urine although it may contain no blood or pus. This is a true bacilluria. It is rarely present after the disease has passed the active stage, yet occasionally it is a permanent condition and the individual is referred to as a "carrier." In these acute infectious diseases the specific organism as well as other bacteria may produce at any time true inflammatory diseases of the urinary tract, which may be the only involvement or may be concomitant with the bacteriuria. Naturally, inflammatory diseases of the sinuses, tonsils, or even the urethra permit the entrance of bacteria into the blood stream, where they may be productive of emboli, or may be simply eliminated by the kidneys. Bacteriuria has been frequently traced to focal conditions such as these. Furthermore, organs involved in inflammatory processes adjacent to or in immediate neighborhood of the urinary organs—and anatomical studies have shown their direct lymphatic connection with the urinary organs, as the colon with the kidney—have been definitely shown to be the source from which bacteria enter the lymph channels and then the kidney by anastomosis of these lymph vessels. Thus, intestinal stasis frequently accounts for the presence of bacillus coli in the urine, according to this most plausible explanation, which is so well grounded on accurate observation that it can scarcely be questioned (lymphogenous bacteriuria).

Here also the question arises as to why bacteria are pathogenic at certain times and non-pathogenic at others. While bacteriuria is supposed to occur under conditions similar to those in inflammatory diseases, we are not dealing here, supposedly, with evident microscopic changes present in the tissues, though it may be more reasonable to assume that an inflammatory condition previously existing has subsided allowing definite changes to remain, which permit of the passage of bacteria. For this reason, with prepared ground, so to say, the relapses showing inflammatory signs and symptoms during the course of bacteriuria are easily accounted for in some cases. Whether or not bacteriuria is simply a sign or manifestation of disease, either in or out of the urinary tract, it is certainly worthy of attention from this point of view and is of utmost importance in the question of treatment.

Symptoms.—The presence of a numerous quantity of bacteria in the urine commonly gives it a turbid appearance and when closely inspected it is of a pale, vaporous character, appearing like a bouillon

culture or suspension of bacteria in other fluid media. If such urine be centrifuged any pus present will be thrown down in the form of sediment, while the vaporous character of the urine is unchanged, being due entirely to the suspension of the microörganisms. It has a vapid odor and is commonly of acid reaction; there is seldom any increase in the cellular elements. The chief and frequently the only symptom present is the character of the urine just described. In a smaller number of cases there are other symptoms, such as frequency of micturition or incontinence and rarely malaise, headache and slight fever. Intestinal disturbances are rather common and their rôle as important etiologic factors must not be overlooked. They were present in one-half of Mellen's cases, and while of the earlier cases 11 were in female children and one in a boy, Mellen's cases were equally divided between the sexes, five occurring in boys and five in girls. Cases reported earlier were in children between the ages of 15 months and 13 years, while of Mellen's cases, nine were in children between five months and four years and one patient was 10 years of age. This emphasizes that the younger the child the greater the pre-disposition toward this disease, a great many cases being found in infancy. In one of Mellen's cases bacteriuria followed immediately a large abscess in the anal region. After the incision of the abscess the bacteria promptly disappeared from the urine.*

The exciting cause is usually bacillus coli communis, which is present in 8 out of 10 cases, the other 2 being staphylococcus albus (Mellen). In all cases only one type of bacteria was found. *Bacteriuria post-vaccinationem* has been reported by M. Petersen† in a two year old girl; 10 days after vaccination a typical bacilluria appeared which the author attributed to contamination of the vaccine with bacillus coli.

Treatment.—The aim should be whenever possible to find and remove the causative factor. When tumors, calculi or foci of infection in the urinary tract or in neighboring organs are found they must of necessity be removed. It is the author's opinion that if cystoscopy and ureteral catheterization as well as cultural methods are more generally employed it will be found that we quite frequently are dealing with a pyelitis or pyelocystitis. In these cases the customary medical treatment is to be carried out by the administration of alkalies for a short time when the urine is acid, then hexamethylenamin is to be given. When there is pain, tenesmus, etc., hot applications and hip baths are of value, as in cystitis generally. It is not objectionable to treat the bladder locally, and boric acid solution, argyrol or preparations of this kind, or weak nitrate of silver solutions may be used for irrigation. Diet and correction of digestive disturbances are of importance. Salol or other intestinal antiseptics may be given.

Prognosis.—The prognosis in children is usually good.

Tuberculosis of the Bladder.—Primary tuberculosis of the bladder in infancy and early childhood is practically unknown.

* Mellen.

† Petersen, M., Ugeskr. f. Laeger (1906), p. 433.

It has been found, as in adults, the result of a descending infection of the kidneys and kidney pelvis, the bacilli reaching the bladder through the urine. Ascending infection is also possible, but extremely rare in childhood, in cases of urogenital tuberculosis with involvement of the epididymis, vas deferens, seminal vesicle and prostate. In these cases the process most commonly extends from the epididymis along the vas and upward into the bladder.

Symptoms.—Clinically the symptoms are those of chronic cystitis, but usually with extreme pain and hematuria, *cystite douloureux* of the French.

Pathology.—The characteristic pathologic anatomical changes are most commonly found involving the region of the openings of the ureters or the urethral orifice and may involve most markedly the right or left ureteral orifice depending upon the implication of one or the other kidney. At first, on the surface of the mucosa isolated or clustered tubercles are noticed, beginning as subepithelial lesions, having the appearance of grayish granulations or grayish-yellow cheesy nodules, of lentil size or larger. As degenerative changes take place the center of the nodules becomes excavated and a tuberculous ulcer develops with ragged, undermined edges. These isolated ulcers later coalesce and the bladder mucosa becomes more generally involved, pronounced changes resulting from infiltration and extension of the ulcerative process. In extreme cases the bladder wall may be covered with ragged debris and cheesy, floating masses of tissue.

Cystoscopy and finding tubercle bacilli in the urine confirm the diagnosis.

Cystoscopy is invaluable in the diagnosis of this condition, but should be carried out with the utmost gentleness and care, with thorough asepsis and antisepsis. A slight traumatism or excoriation may be the starting point of most active ulcerative processes in the bladder, so that extreme care in the preparation of the patient and the instruments should be taken.

It might be stated that in cases of acute miliary tuberculosis the bladder has been known to become involved just as any of the other organs.

Paralytic Bladder.—This condition may follow injuries or diseases of the cord. In cases in which retention follows, and I particularly refer to cases of anterior poliomyelitis and spina bifida though it is not uncommon to find retention of urine in typhoid fever or, as at present, in influenza, the question arises as to the best plan of treatment. Murphy and Beasley advise, in connection with injuries to the cord, allowing the bladder to become distended and permit overflow. I have been permitted to see the results of back-pressure in cases of acute infection and it always results in death. In these cases pain may often be absent in the beginning. In diseases of the cord, however, the pain may be excruciating. This in itself, in my opinion, might be sufficient indication for catheterization, but considering the well-known effects of back-pressure persisting for any length of time,

I believe that catheterization is imperative. This naturally should be carried out systematically at least twice a day, with all surgical precautions in this mode of interference. The bladder should be irrigated each time with boric acid solution. As spontaneous urination sets in the number of catheterizations are lessened until as normal function returns. Naturally if conditions are favorable to it, infection may occur and produce a cystitis. The usual treatment may be instituted if this becomes necessary. In retention of urine during typoid fever and influenza the treatment is the same as already outlined.

Retention of Urine.—Etiology.—Retention of urine may result in all those conditions in which micturition is accompanied by pain. It may also result from deformities and anomalies of structure, congenital stricture, duplications of mucous membrane of urinary tract, calculi, inflammations of the kidney, bladder, prostate, urethra or prepuce, in pericystitis, congenital hypertrophy of the prostate, foreign bodies and new formations in the urinary organs, prolapse of the vesical mucous membrane, paresis of the bladder in stupor in the infectious diseases, in organic diseases of brain and spinal cord, and further by mechanical and reflex disturbances or new growths in the neighboring organs (for example, periprostatic abscess). Retention of urine may be simulated in babies or in children suffering from serious gastro-intestinal diseases who take but little nourishment and suffer with numerous watery evacuations of the bowels.

Symptoms.—Patients, generally young children, have the pale, pasty appearance of nephritis. Usually there is difficulty in urinating. Abdominal palpation reveals a large globular mass in the hypogastrium, which is the distended bladder, containing often from 6 to 10 ounces of purulent urine. As secondary developments, ureters and kidneys dilate and unilateral or bilateral hydronephrosis results. The condition is frequently that of spasm, that is, disharmony between detrusor and sphincter muscles. Cystoscopy shows dilated ureteral orifices.

Prognosis.—The prognosis is good in organic cases, but bad in the neuromuscular group.

Treatment.—In the latter group the treatment is palliative, bladder irrigation, cystostomy, or nephrotomy. Nephrectomy is out of the question, as in practically all cases both kidneys are involved.

Hyman* reports a case in a child, three years of age. There had been constant dribbling of urine from birth. There had been no gain in weight for six months prior to examination. The urine contained pus. Hypospadias and pinpoint meatus were present and the bladder could be felt at the level of the umbilicus. No obstruction was encountered by the catheter and 12 ounces of cloudy, alkaline urine were obtained. Pyelography demonstrated marked dilatation of tortuous right ureter and a considerable degree of hydronephrosis.

This condition is infrequent and is probably often overlooked or found only at operations for other conditions, such as appendicitis,

* Internat. Jour. of Surg., July, 1919.

pelvic abscess, etc. Several similar cases were reported by Beer several years ago, and others appeared more recently in the literature.

Spasms of the Bladder.—Bokai states that spasms of the bladder have been observed in the newborn and in these instances must be regarded as reflex in origin and of a physiologic nature. In older children spasms of the bladder have been observed following exposure to cold, wetting of the feet, etc.

Fig. 183.—Illustrating bladder tumor. (From Albarran.)

Tumors of the Bladder.—Bladder growths in infancy and childhood, from statistics at hand, are decidedly rare. In the older literature reports of bladder tumors are few and Gurlt in 1876 notes that of 16,637 cases of tumors of various organs seen in the three Vienna hospitals, there were only 66 or 0.39 per cent. involving the bladder. Still rarer are reports of these tumors in children and Bokai in 1878 considered them as not only clinic but also anatomico-pathologic rarities.

From a survey of the literature of collected cases I offer the following conclusions:

The great majority of all tumors in childhood occur during the first five years of life. After this a decided fall in the number of cases occurs up to the age of 17. All the tumors, with notable and decidedly rare exceptions, are of the connective tissue and muscular type and the large majority are malignant. Sarcomata predominate among the malignant forms and fibromyomata seem most common of the so-called benign tumors. Practically all tumors in children must be considered potentially, if not pathologically, malignant, as in the adult, and clinically have one point in common, being almost uniformly fatal if left untreated. The comparatively infrequent and late appearance of hematuria, one of the cardinal and early symptoms of bladder tumor in adults, may account for the extremely bad prognosis in all these tumors in children as early diagnosis is rendered much more difficult. The vast majority of primary growths in children are polypoid in character.

The tumors which have been found in the young are:

Sarcoma (spindle- and round-celled).
Lymphosarcoma.
Fibrosarcoma.
Myxoma.
Myxosarcoma.
Fibrosarcoma.

Mixed tumors:

Fibroma-oedematosum-myo-enchondromatosum (Kaufman). The first tumor, according to Husler, in a child's bladder in which inclusion of cartilage was shown.
Dermoid cysts.
Angioma (of rectum or bladder—case reported by Judd).
Telangiectic fibrous polypus (Rabitchek).
Cancer (one case only, reported by Judd).
Papillomata, so-called, benign or simple (F. S. Watson, Koll and Spangara).
Myxoma—frequently called polyp.
Rhabdomyoma—fibro-rhabdomyoma and myxomatous rhabdomyoma (Cattani).
Fibro-adenoma (von Frisch).

Tumors usually arise from the mucosa or submucosa and are commonly located near the trigone or around the internal urethral orifice. They may be single or multiple, pedunculated or sessile and vary greatly in size. There may be one single small or large tumor which may have a lobulated appearance, like a bunch of grapes and may fill the entire bladder. Their tendency is to recur rapidly but not to form metastases. They may invade surrounding organs and tissues, as the vagina, uterus or vulva, prostate or abdominal wall. They tend to infiltrate the mucosa and submucosa of the bladder, causing thickening of the bladder wall. Hypertrophy of the muscularis and trabeculization frequently occur because of interference with urination. There may be obstruction of or involvement of the ureteral orifices and these may be displaced; consequently, a one-sided or bilateral

hydronephrosis is common. The tumor grows into the bladder and then pushes into the urethra and partly through the same, causing dilatation of the urethra, especially characteristic in girls; in them also frequently pushing the vagina forward. In boys the bladder grows *in toto*, so that it frequently has the appearance of a filled bladder, being palpated in the median line of the abdomen as an oval tumor, soft or fluctuating in consistency, and the upper part at times reaching to the umbilicus.

Some important conclusions reached by Husler as a result of a study of 14 cases collected by him from the literature, and which are generally in accord with conclusions arrived at by Steinmetz and other observers, are as follows:

Sarcoma.—Five cases occurred in boys and one in a girl. All were multiple and appeared in various forms, grape-like or lobulated, cauliflower-like or consisting of single nodules or flattened elevations, mostly sessile, rarely pedunculated. In two or three cases the lower one-third of the bladder was involved, the size of a hazelnut to a fist. The surface was mostly smooth, rarely (one case only) nodular. In no case were there ulcerations or necrosis of extensive degree. Superficial erosions were not rare. The growth was always rapid; bleeding very trifling. There were no metastases.

Benign Tumors.—Seven cases were reported. *Fibro-adenoma.*—Only one case was known to this date (1905). The tumor probably originated from the glands of the posterior urethra.

Myxoma.—This type is very rare. Fibromyxomata and myxosarcoma are more common. Macroscopically and in clinic manifestations these approach the sarcomata (Steinmetz and Albarron), while fibromyxomata are much more benign and resemble more the true fibromata. Sarcoma and myxomata merge into each other and may resemble the polyps of the nose. Albarron examined two myxomata histologically and had to classify them with the sarcomata. They are distinguished by great malignancy and their galloping course.

General Conditions of Benign Tumors.—Of the seven cases reported, six occurred in boys and one in a girl. They were multiple, with one exception, and pedunculated, grape-like, cauliflower-like or polypoid, consistency partially hard, partially soft, usually glistening and smooth of surface, located without exception in the trigone, right or left, or near the neck of the bladder. In all cases one or more lobulated processes were found in the urethra or vulva. Size is very variable, but mostly the tumor filled two-thirds of the bladder. Growth is not rapid. Complications of the kidneys were common.

The clinic picture in tumors of the bladder is usually as follows: Without prodromes, in a previously apparently healthy child difficulty of urination appears, gradually increasing in severity and often accompanied by great urgency and tenesmus. The onset may be also associated with dribbling or incontinence or partial or complete retention. There may be sudden stoppage of the urinary flow and the child may be obliged to void urine in unusual positions or may find it easier to void

in the recumbent position. Pain is almost always present and may be either slight or intense. It is usually referred to the neck of the bladder or urethra and is especially marked at the time of urination. Pain in the hypogastrium and groin is frequently complained of. The amount of urine as compared with the distention of the bladder is small, even when the catheter is resorted to. The catheter usually meets with a definite obstruction and in an attempt to irrigate the bladder only a few cubic centimeters of fluid will enter. The urine at first is usually negative. Pus, mucus, and perhaps blood, appear as cystitis develops. Albumin is present in practically two-thirds of the cases, together with more or less mucous and bladder epithelium. Parts of the tumor may pass with the urine; the odor is frequently offensive and may be ammoniacal. Hematuria is frequently absent, as ulceration is usually late in these types of tumor. The symptoms may strongly resemble those of vesical calculus.

Tumors that infringe on the internal urethral orifice may give rise to urinary symptoms as well as to hematuria. These are usually papillomata. However, if the papilloma is situated in the fundus or wall of the bladder, it may reach considerable size before urinary symptoms set in. Malignant tumors, particularly sarcomata, are comparatively rapid in growth and when they involve a considerable portion of the bladder area urinary symptoms set in.

Diagnosis.—Tumors have been found spontaneously protruding from the urethra in female children. The diagnosis is usually difficult in the early stages. The child's bladder is readily palpable and a mass in the hypogastrium with symptoms as previously described, especially pain and dysuria in the absence of congenital stricture, should enable one to make a tentative diagnosis. The cystoscope is invaluable, especially in older children. Roentgen-ray examination is of assistance in some of the harder types of tumors. Cystography can be used as in the adult. Cystoscopy can be carried out in female children as early as six weeks of age, as has been reported. In the male we have cystoscoped patients in the first year of life. In cases of hematuria early cystoscopy is indicated in order to establish a definite diagnosis. In a few cases of sarcoma observed, cystoscopy could not be carried out because of inability to distend the bladder, due to the enormous involvement of the bladder wall. In these cases abdominal palpation as well as bi-manual palpation per rectum reveals a large rounded mass, which may be entirely movable or may give the sensation of a distended bladder, but on the introduction of the catheter no urine can be obtained.

Treatment.—The treatment is entirely surgical except for the palliative treatment which may be instituted until diagnosis and treatment are decided. Unquestionably, benign tumors should, if possible, be treated with the high frequency current. This however, cannot be carried out in many instances. In these cases a suprapubic cystotomy, excision either with cauterization or diathermy and suturing of the base, may be performed unless the tumor is so favorably located

that a resection can be performed. I would advise complete resection in the malignant cases, especially sarcomata. Naturally all the ordinary surgical pre-operative and post-operative care should be given.

Course and Prognosis.—The course and prognosis depend entirely on the location and the character of the involvement. The papillomata which are considered benign may exist unquestionably for a long period of time and yet offer the most favorable prognosis of all neoplasms. As regards malignant tumors, sarcomata are more frequent than carcinomata and their prognosis when treated surgically is much more favorable. The author removed practically the entire bladder from a youthful individual and the patient is absolutely well 15 years after operation.

Malakoplakie (or cystite en plaques).—The etiology of this condition is unknown. It is exceptionally uncommon in children and has been examined in only a few instances. Hanselmann considered it a type of chronic cystitis, possibly localized, as it occurs in areas round in outline, of varying size, of a dirty-yellow color, and surrounded with a light-pink zone. Microscopically distinct inflammatory infiltrations are found.

Leukoplakia.—This is practically the same condition. However the process is more diffuse, even extending into the ureters and urethra, the appearance being pearly. The relationship of these two conditions to other diseases of the urinary tract is unknown.

Hypertrophy and Dilatation.—In connection with obstruction to the outflow of urine as well as to irritation of the bladder from inflammations, tumors, stone, foreign bodies, etc., the work of the bladder wall is increased, leading to hypertrophy. At first there may be a thickening of the bladder wall and a tendency to trabeculization, which naturally means that muscle bundles become prominent, due to excessive work. In some instances the bladder becomes concentrically hypertrophied to such an extent that the bladder capacity becomes markedly diminished. When this condition continues for any length of time the capacity and retention of urine become greater and the bladder becomes dilated. If the dilatation exceeds the muscular power of the concentric hypertrophy, the bladder becomes so greatly distended that it becomes atonic. Naturally in these cases the muscular bundles that produce the trabeculization allow of formation of diverticuli and pockets.

CHAPTER CV

CYSTOSCOPY—CATHETERIZATION

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In addition to the usual methods of examination for disease conditions involving the genito-urinary tract of both male and female children, the more modern methods of roentgenology, cystoscopy, ureteral catheterization, examination of the separately collected urines and their estimation by the different functional tests should be employed in selected cases. The more expert the examiner, the more readily can these methods be carried out. In the adult the indications are more numerous but in individual cases, whether in the child or in the adult, the need is for accurate diagnosis. Cystoscopy can be performed in the female in the first weeks of life. In the male it is not easily done; however, it has been used sufficiently often in the first years of life to demonstrate its efficiency. The older the children the greater the ease with which cystoscopy and its adjuvants can be utilized. I believe that these methods are more commonly applied after the first years of life. I believe also that cystoscopy and ureteral catheterization are practical and essential aids in correctly making an early diagnosis in certain conditions which otherwise would be either overlooked or diagnosed too late to be helped. I venture to state that the vast majority of pediatricians are not trained to use these methods, nor are the genito-urinary surgeons offered the proper opportunity and they, therefore, also lack the necessary experience, consequently I urge that there be a fuller coöperation in these matters as it can only be to the interest of the afflicted.

The instrumentarium necessary for the examination of children is rather limited. It consists of a plain examining cystoscope of the smallest caliber made—12 Ch. With children more developed one of 15 Ch. is of greater advantage. In all the work carried out in children, which has come under my observation a Nitze instrument has been used, having the proper caliber and fitted with a lens so that it can be introduced and the bladder distended with 50 c.c. or more of clear fluid, water being the usual medium.

Ureteral catheterization is carried out, as a rule, with instruments which allow the passage of only one catheter. When older children are catheterized a double catheterization instrument may be introduced. The most useful instruments are the *Brenner*, with the catheter arrangement just below the optical portion. This permits of direct

catheterization, while the *Albarran-Nitze* or the *Brown-Buerger* cystoscopes permit of *indirect catheterization*.

For details of construction of these and other instruments which those who are interested may prefer to use, the various textbooks on cytsoscopy may be consulted, as the space allotted to this subject permits me to give only a brief outline concerning instruments and methods as used by me in this line of work.

The same principles are applied as in adults.

Preparation of Patient.—Functions are made active, laxatives are given if necessary the night before examination, if not otherwise contra-indicated, and an enema is given an hour before examination. Besides, fluids in sufficient quantities are given up to one hour before examination. As a rule warm daily baths are advised in order to keep the skin active. Children as a rule require an anesthetic, yet I have made cystoscopic examinations both in the male and female without a general anesthetic. Local anesthetics may be used on older children with advantage.

The introduction of a cystoscope is always difficult. In the female, preliminary dilatation of the urethra with straight sounds is always desirable. In the male oftentimes a meatotomy is necessary and dilatation of the urethra with bougies. The lubricant must be miscible with water.

No particular attention as to position is necessary with children. Naturally, the supine position is the easiest to assume. In older children a lithotomy position is oftentimes best.

As to preparation, the field of work, the instruments as well as all utensils which come in contact with the patient, must be sterilized. The operator should govern himself according to all surgical principles. These precautions should never be neglected.

After cystoscopy, as well as ureteral catheterization, the little patients must be given every care. Wrap them in warm blankets and give fluids as soon as possible. When catheters are allowed to remain until sufficient urine is collected, they must be held firmly in place and care taken that children cannot remove them.

Acute inflammations of the urethra and bladder are contra-indications for urethral instrumentation—whether it be the passage of cystoscope or other instrument for diagnostic purposes. These are rather unusual in children, although gonorrhea is found in both sexes and this is the common cause of acute inflammation. Naturally the general condition must be considered, and it is scarcely necessary to state that in grave cases, due to sepsis, hemorrhage, or general cachexia, instrumental examinations can only be employed if other methods do not permit a probable diagnosis to be made.

Roentgen examinations should never be neglected with children. Whenever an obscure urinary condition exists an *x*-ray examination should be a part of the routine. Repeated examinations are desirable as the presence of urinary calculi is readily noted by means of the *x*-ray but in a small percentage of cases they may be overlooked. As a rule,

good negatives can be obtained and in most children definite outlines of the psoas muscles as well as the kidney are to be expected. The size, contour and location of the kidneys should always appear on the plates.

I have found cystography helpful in establishing a diagnosis in some instances in which cystoscopy could not be carried out. This consists of injecting into the bladder, after the spontaneous passage of urine or after bladder catheterization, a 10 per cent. solution of thorium. The quantity injected depends on the distensibility of the bladder. Often 75 c.c. or more have been introduced by the gravity method. Congenital diverticula, open urachus and even congenital dilated ureters with involvement of the pelves of the kidney or distorted bladder, have been diagnosed by this method.

Cystoscopy at once informs the examiner of malformations such as diverticula, gaping ureteral orifices, usually indicative of dilated ureters, and of the presence of calculi or growths; chromocystoscopy of the rapidity and intensity with which the dye appears from either or both ureteral orifices is also of value.

Ureteral catheterization may be carried out by *x*-ray catheters, as suggested by Kolischer and Schmidt in 1901. After they are introduced the exposure is made and definite information may be derived from the examination.

If ureteral catheterization is carried out only on the suspected side, the urine should be collected and submitted to all of the usual tests. The urine obtained by means of a catheter introduced into the bladder by the side of the ureteral catheter should show the condition of the opposite side. If the age of the patient permits of double ureteral catheterization this substitute method need not be practiced.

After the collection of sufficient urine from each side, the ordinary functional tests can be made. The phenolsulphonephthalein, or so-called phthalein test, should be used. It consists of injecting intravenously or subcutaneously 1 c.c. of a physiologically standardized solution of phthalein, rating the time of its appearance on either side and collecting 15 minute specimens, two or three on each side, estimating the quality of dye excreted in these periods.

Urines may be collected through the *x*-ray catheters if these have been inserted; naturally the dye tests are also carried out.

Pyelography, or making the upper urinary tract opaque to the *x*-rays by various media, may be considered as necessary in selected cases. I refer to those cases in which a cystoscopic examination, ureteral catheterization, roentgenogram, and the usual methods of examination still leave the physician in doubt. I prefer to use a 20 per cent. sodium bromide or 13 per cent. sodium iodide solution and it is to be injected by the gravity method. Naturally care must be taken not to overdistend the kidney pelves.

In older children, whenever deemed applicable, some therapeutic measures may be applied with the aid of the cystoscope and ureteral catheter. The more important are the fulguration treatment of benign papillomata of the bladder done with the aid of a ureteral

catheterization cystoscope. Then the lavage of the pelvis of an infected kidney. In these cases of pyelitis much has been accomplished by treatment with the various silver salts.

Nowadays sounding the bladder for stone or tumor is obsolete, as roentgenograms and the cystoscope give a more accurate result. Even though they possess a special curve and are fitted with a sounding dial they are not to be used to the exclusion of the cystoscope. A sound should be used only when the cystoscope is not at hand or if the *x*-rays do not show the prescence of a stone.

No matter whether cystoscopy, sound or catheter is used for diagnosis or therapeutic use, the principles of asepsis as given for the use of the cystoscope must be practiced. Any of these procedures must be carried out under stringent precautions, even if infection is already present.

Whenever catheterization is indicated the attempt should always be made to pass a soft-rubber catheter of suitable size. If this is unsuccessful, a French catheter which will assume the normal curvature of the urethra, but can overcome a slight resistance, should be tried. If failure still occurs a metal catheter should be inserted. It has been my experience that institutions for the care of children do not always have the necessary equipment to enable this work to be done as it should be.

In male children in the first years of life, oftentimes the use of a ureteral catheter avoids necessity for using a metal instrument.

If for some reason it is impossible to pass a catheter in order to relieve a patient of retention, a suprapubic puncture may be made with a small trochar. In children the bladder may distend to immense proportions. In them the bladder is high anatomically and with it rises the peritoneal fold, so that one need not fear the peritoneum if the puncture is made 2 to 3 cm. above the pubes. The ordinary surgical technique is necessary.

Whether the bladder be entered with trochar or catheter, all the urine should *not* be drawn off *at one time*. A small quantity at a time not a few hundred cubic centimeters should be taken until the bladder is emptied and then 100 c.c. of saturated boric acid solution should be introduced so as to prevent collapse of the vessels which cannot retract so quickly as the muscles of the bladder, and in order to avoid hemorrhage. Whenever it is difficult to catheterize or when it has become necessary to use a trochar it should be made permanent, that is, they should be fastened so as to avoid further instrumentation. Besides, a stop-cock arrangement can be made in order to allow the withdrawal of urine whenever deemed necessary.

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CHAPTER CVI

DISEASES OF THE MALE GENITALIA—TESTICLES

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Orchiepididymitis.—Inflammations of the testicle and epididymis are rare in children. They may be acute or chronic and due to either traumatism or infection.

Inflammation of the testicle in children is almost always due to infection. The spermatic gland may be infected by microbes reaching it from the exterior either by an accidental or operative wound, but the infective process is more often the extension of some general infection.

There are different routes by which the infective agent may reach the testicle:

1. By its excretory canal, the canal of the vas.
2. By its arteriovascular apparatus or by the spermatic veins.
3. By the lymph glands.
4. By the vaginal serosa.
5. By the connective tissue of the scrotum.

Infection may follow mumps, variola, typhoid, tuberculosis, gonorrhea, tonsillitis, influenza, pneumonia, scarlatina, diphtheria, and septicemia. The diseases in which it is most frequently encountered are mumps, variola, tuberculosis and congenital syphilis.

In mumps, rarely, it may be the only clinical manifestation of the disease. Beardsly reports a case in a boy, 11 years of age, who was exposed to mumps and eight days later developed a well-marked case of orchitis, it being the only clinical manifestation.

In smallpox, Chiari and Bérand claim it is a frequent complication in children, as they were able to collect numerous reports in the literature.

Tuberculous orchiepididymitis in children has been reported as primary, and as secondary to tuberculosis in other organs and structures of the body.

Syphilitic involvement of the testicle and epididymis in congenital syphilis is well known. Hutinel makes the statement that the testicle is involved in one-third of the cases of congenital syphilis in male children.

Epididymo-orchitis as a complication of gonorrheal urethritis in children does occur, but is relatively infrequent. Mitchell reports a case of gonorrheal epididymitis in an infant, four and one-half months of age, and in a review of the literature be found 133 cases of gonorrheal urethritis in male children. Among these only three were complicated

by epididymitis, one in an infant who developed epididymitis on the twenty-sixth day, 12 days after developing urethritis. Death followed on the sixth day of the complication, or on the thirty-second day of life. The other two were in children of 16 months and two years respectively.

Orchiepididymitis in the course of typhoid, scarlatina, rheumatism, tonsillitis, and influenza in children is rare.

Ombredanne has called attention to the occurrence of acute primary orchitis in children in their teens. He had seven such cases. He gives torsion of the cord as the etiologic factor. He found this condition unquestionably in four of his cases and doubtful in two others.

Treatment.—As a general rule orchiepididymitis in children yields to local treatment and rest. With hot baths, hot compresses, suspension, and absolute rest in bed resolution usually takes place in a few days. Atrophy of the testicle has followed and should always be considered in giving a prognosis.

Abscess may develop in cases of orchiepididymitis following trauma and Gragnot reports a case of abscess developing in a case of orchitis complicating mumps in which the aspirated pus gave pure streptococci on culture.

Abscess should be treated on surgical principles with incision and drainage.

The iodids and salicylates may be given in the acute inflammatory conditions, the former in small doses to promote absorption, the latter in fair-sized doses to alleviate pain and fever. It also promotes diaphoresis.

The diet should be liquid and an abundance of water should be given during the febrile stage.

A local application of guiacol, 25 to 50 per cent., in olive oil may be made once daily, or ichthyol, 10 to 30 per cent. strength, in petrolatum, may be applied twice daily in cases in which it is impossible to keep the hot applications in place.

Tuberculous Orchiepididymitis.—Tuberculous orchiepididymitis in children is of rather infrequent occurrence, according to reports of large clinics. Broca observed it in 44 out of 46,600 cases and Hawart reports 158 cases in 56,000 boys examined in a London hospital. According to most authors it occurs in the first period of childhood, that is in the first seven years. Poisonner in 1907 collected 91 cases in children under 15 years of age, 42 in which it was noted under two years of age, and 49 between 2 and 15 years of age. Broca states that is is most common in the first two years of life. (This is according to the 44 cases observed in his service. Julien reports 20 cases observed in Lanneulogue's clinic, six at one year of age, six at two, five from two to seven, one at seven, one at 12½, and one at 13 years. In Hawart's cases, nine were under 12 years of age and 146 over 12 years.)

The disease may be primary in the epididymis or testicle, or secondary to tuberculous affections elsewhere in the body, especially tuberculosis of the bones, and peritoneal tuberculosis.

Family pre-disposition seems to play a part. That children have been born with tuberculous affections of the testicle has been demonstrated, the infection being transmitted through the placental circulation. Dreschfeld observed a case of congenital tuberculosis of the testicle. Giraldi recorded two cases of tuberculosis of the testis in infants a few days old.

Clinically two types may be described, one of acute onset, with swelling, redness, edema, fluctuation, the skin becoming adherent early, and spontaneous rupture, all of which may occur within a few weeks. In this variety pain is usually a prominent symptom. The epididymis, testicle and skin are all involved in one mass, it being often impossible to distinguish the epididymis from the testicle.

The other type is of slow onset, with painless, hard, nodular swelling of the epididymis, in which it may remain localized. When softening takes place the condition is much more likely to be localized. Lyons reports two such cases, one in a child of seven months and the other in a child, 16 months of age, in which the infection was localized in the epididymis, forming abscesses which were incised and which healed after several months. Both patients were well four and four and a half years later respectively, this being the only tubercular focus that was demonstrable.

The more acute and rapidly advancing form is almost invariably encountered in young children.

Tuberculosis of the epididymis and testicle in children differs in three ways from the disease as found in the adult:

1. The disease is usually much more rapid in children, that is, there is much earlier abscess formation.

2. The testicle shows early involvement more often—in some cases there is an apparently simultaneous involvement of the epididymis and testis. Julien states that at times the testicle is seriously involved, the epididymis being apparently free from infection. Practically every case in adult life has its inception in the epididymis.

3. That in the majority of primary cases of tuberculosis in the epididymis and testicle there is no involvement of seminal vesicles, prostate and bladder.

Symptoms.—Symptoms may be practically lacking, the condition being discovered by the mother or nurse when bathing the child—finding a swelling in the scrotum. The child may be slightly ill, or peevish, with a slight fever, or in cases of slow onset there may be no subjective symptoms. In the acute form there will be considerable pain, swelling, and temperature.

Diagnosis.—The diagnosis will depend on the elimination of certain conditions, chiefly, congenital syphilis, new growths, and the epididymo-orchitis encountered in the infectious diseases.

Usually, in congenital syphilis, other demonstrable conditions point to lues; second, more often the testis alone is involved; third, the swelling is smooth, hard, and non-painful; fourth, the Wassermann reaction; and fifth, the therapeutic test—if the condition subsides

or grows better under specific treatment one can conclude there is at least a syphilitic basis, but this does not exclude tuberculosis unless all structures return to normal.

In tumors there is usually slow growth, no involvement of the overlying skin, and the cord and epididymis are not involved. In malignant tumors there may be rapid growth and here glandular involvement is usually found. The tuberculin test—von Pirquet or the subcutaneous injection—and the temperature observation should exclude new growths. Tumors are much more rare than tuberculosis.

In epididymitis and orchitis developing during or following the acute infectious diseases there is usually the history of the disease, the onset is abrupt, temperature, pain and tenderness to manipulation arising all within a few hours. Abscess formation is rare. The condition usually rapidly subsides upon rest and treatment.

Rectal examination should never be neglected in cases of suspected tuberculosis, as the involvement of the seminal vesicles and prostate, which are hard and nodular, practically confirms the diagnosis of tuberculosis.

Prognosis.—Practically all authors agree that in primary tuberculosis of the epididymis and testicle in children the prognosis for a symptomatic cure is good, that is, the disease will become arrested and stay confined to the original foci, providing the treatment in all respects is correct. In tuberculosis secondary to tuberculosis in other parts of the body the prognosis should be guarded, that is, the outlook is grave.

Treatment.—Treatment should include all the hygienic, dietetic and climatic measures given the patient suffering from pulmonary tuberculosis, proper food, clothing, rest, fresh air, and sunshine.

Tuberculin cautiously and judiciously given is probably the most efficient single therapeutic measure. The beginning dose should be small and slowly increased, carefully avoiding reactions, and should be given over a considerable length of time at from five to seven day periods.

Surgical treatment should be conservative. Local abscess should be treated on the surgical principles of incision and drainage; fistulous tracts, by curettement or actual cautery, with iodoform or iodin swabbing, and iodoform and dry dressings.

In cases of hopelessly involved epididymis and testis in which the patient is not responding to treatment, castration is to be seriously considered.

Injuries of the Testis.—There are three kinds of injuries of the testicle: (1) Dislocations, (2) contusions, (3) wounds.

Dislocation or luxation of the testicle is the result of traumatism which acts directly on the organ, squeezing it upward and to one or the other side.

Treatment.—If seen after the accident, attempts at reduction by manipulation should be made, and if the pain is severe an anesthetic

should be given. If not seen until some time has elapsed adhesions will have formed which will prevent reduction by manipulation, and render operation necessary.

In any cases of this injury the testis is very liable to atrophy because of the inflammation and consequent strangulation caused in its blood supply.

Contusions are divided into first, second, and third degree, according to the extent of the trauma.

In first degree injuries there may be a slight degree of laceration of the smaller blood-vessels with effusion of blood into the parenchyma of the gland and also some effusion into the tunica vaginalis.

In the second degree, in addition to the foregoing, laceration of the seminal tubules may occur. In this degree abscess and atrophy are apt to occur.

In the third degree the lesions are more extensive and there is always atrophy of the gland.

Symptoms.—Severe pain, accompanied by all the signs of shock. Swelling immediately appears, with ecchymosis and signs of fluid in the scrotum, depending on the degree of injury.

Treatment.—Stimulants should be given and heat applied for the shock; when effusion is rapid cold compresses or ice bags should be applied for several hours. The patient should be kept in bed until all pain has ceased. He may then be allowed to be up and about, having the testis well supported. If an abscess forms, it should be incised and drained. If there is an accumulation of blood clots, this should be evacuated and adequate drainage established.

Wounds.—These may be incised, punctured, or lacerated. The treatment will depend on the amount of destruction the organ has suffered. Emergency treatment consists in carefully cleansing the parts and applying moist dressing with good support. This treatment should be used also in ordinary lacerations and punctured wounds. After carefully trimming the edges of the *laceration* it should be sutured and drainage established. In *incised* wounds, after careful cleansing, the tunica and scrotum should be sutured, with adequate drainage, and moist or dry dressings applied. A good supporting bandage is necessary in all these injuries.

Needless to say, it is good surgery to administer a prophylactic dose of antitetanic serum in cases of open wounds of the testis.

Prognosis in wounds depends on the amount of injury to the organ and its blood supply and the severity of the resulting infection.

Atrophy occasionally follows such injuries as a kick or fall astride a fence. The testicle becomes acutely swollen, involving, of course, the epididymis. This is followed by a hydrocele if no hematocele is produced at the time of injury. In either instance, if the injury does not destroy the circulation, the swelling gradually subsides, the hydrocele may disappear and later on atrophy of the testicle may be complete. No matter whether cold packs are applied at once and applications of heat are made later, the end results are the same. No

surgical treatment can be instituted. If it is, it usually occasions immediate loss of the testicle.

FIG. 184.—A right testis in Scarpa's triangle. The right half of the scrotum is developed but not distended. From a photograph of a man, aged thirty-five, who said his right testis had always been in this position. (Eccles.)

Ectopic Testis.—Normally the testis descends into the scrotum at from the eighth to the ninth month of fetal life, but Holt states

FIG. 185.—A left testis lying in Scarpa's triangle. Its cord could be traced through the superficial abdominal ring. (Eccles.)

that in his experience in 10 per cent. of male infants at birth, one or both testes were not in the scrotum. Weisberg found in 103 male infants at birth, only 73, or 70 per cent., in which both testes were in

the scrotum. Sachs, in 143 infants from one to four months old, found 86 per cent. in which both testes were in normal place, but the majority reached it only in the first months of post-natal life, and a certain percentage not until the age of puberty. In support of this view Coley's observations are significant. Of 18,410 male children under 14 years of age, applying for treatment for inguinal hernia at the Hospital for Ruptured and Crippled, there were 561 cases of undescended testis, or 3 per cent.; of 3848 boys between 14 and 21 years of age, there were 92 cases, or 2.2 per cent., and of 37,370 men over 21 years old, there were 75 cases or 0.2 per cent

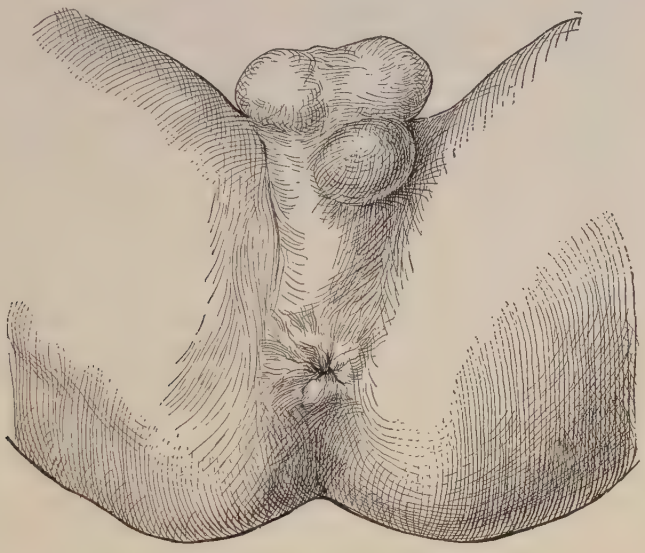

FIG. 186.—Perineal ectopia.

There are three great types:

1. Arrested migration.
2. Aberrant migration.
3. Intermittent migration.

In the first, the testicle is fixed in some abdomino-scrotal location which it had reached in its normal descent.

In aberrant migration, the testicle after remaining more or less fixed in some part of the normal path of descent, deviates by degrees to some neighboring zone.

Intermittent migrations are exceptional. They are due to a complete permeability of the peritoneo-vaginal canal, with a long, free, mobile testicular pedicle.

Arrested migration, in which the testicle remains in the abdomen, is the usual type and is spoken of as cryptorchidism. Monod and Terrillon state its occurrence in 1.25 in 1000 male children.

Bilateral ectopia is rare.

The inguinal type of ectopia is the most frequent (67 per cent.).

Various theories and explanations are given as to the cause of this anomaly. Hunter, and more recently Bland-Sutton, are of the opinion that the condition results from anomalous development of the genital tract in early fetal life. In support of this view, Woods reports one case in which there was an undescended testicle, in which post-mortem examination showed that the kidney on the same side was only a small fibrous tag, the ureter consisted of fibrous strands, and no ureteral opening was present on that side of the bladder. The vesicle was a large, blind pouch, one portion of which protruded into the bladder; neither the epididymis nor vas was attached to the testicle, the vas being represented by a blind tube, 6 cm. in length. He also reports the examination of other cases in which the epididymis was not attached to the testicle and in which the vas was in no way attached but terminated in a series of blind coils.

Buddinger considers the condition as being caused by adhesions, the result of peritonitis in fetal life.

Uffreduzz explains it as a reversion to a lower mammalian type. (In the rabbit and hedgehog the testicles are periodically withdrawn into the abdomen.)

Eisendrath has noticed in these cases a great deficiency in the development of the arching fibers of the internal oblique muscle and a weak conjoined tendon; that a well-developed internal oblique muscle acts as a sphincter to prevent the retraction of the testicles by the cremasteric muscle. He likens the gubernaculum testis to a four-tailed ribbon, the fused end being attached to the lowermost portion of the testis. One of the four is attached over the pubic region, another over Scarpa's triangle, the third to the perineum, and the fourth, usually the best developed, is attached to the lowermost portion of the scrotum. Under normal circumstances the scrotal tail is supposed to pull the testis downward. If this does not occur we may have the testis arrested in its descent (*a*) in the iliac fossa; (*b*) in the inguinal canal; (*c*) just beyond the external ring; and if it is pulled by any one of the three other tails we have *abnormal descent*, femoral, pubic, or perineal variety.

Anatomical conditions of the retained testis as enumerated by Doolin are:

1. Usually it is small and soft.

2. Usually there is a definite separation of the epididymis from the testicle.

3. Usually a well-developed processus vaginalis occurs and it may be occupied by the lower end of the vas which may extend as much as 2 in. below the undescended testis.

4. In practically every case there is a real or potential hernia. Eisendrath describes an interstitial form of hernia, which he states is invariably associated with undescended testicle.

In the report of 126 cases in which operation was performed for undescended testis, Coley states that he was able to demonstrate the hernial sac in every instance.

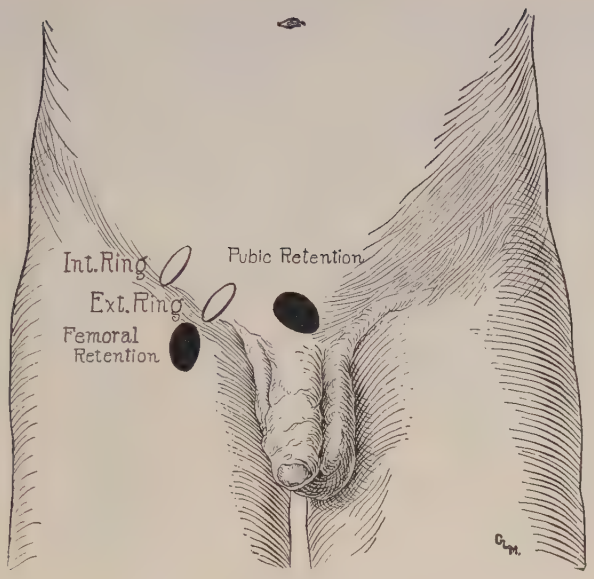

FIG. 187.

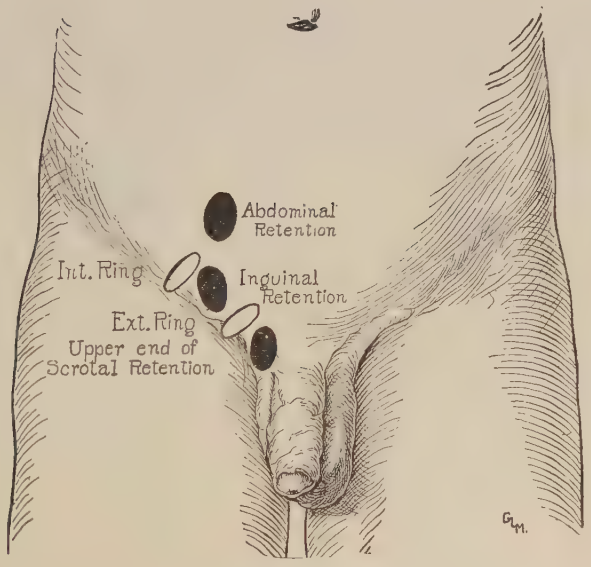

FIG. 188.

FIGS. 187, 188.—Illustrating different locations possible in retention of the ectopic testicle.

The minute anatomy is well described by Odiorne and Simmons, there being two important groups of cells, the spermatogenic cell responsible for secretion of spermatozoa, and the interstitial cell which forms the internal secretion which in turn brings about the sex characteristics. Their conclusions are, that in undescended testis there is great failure of development of the spermatogenic cells, and that the interstitial cells, which in the normal testis are present only

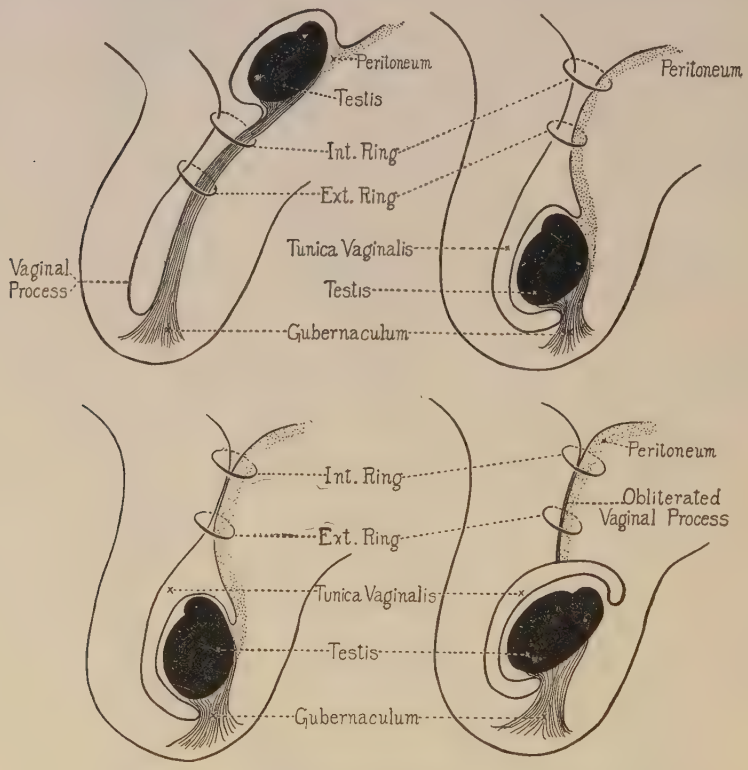

Fig. 189.—Schematic drawing showing descent of testicle into scrotum.

during childhood and disappear about puberty, are greatly increased. Finotti speaks of the great development of these cells in undescended testes and suggests the possibility that their increased growth is responsible for the beginning of teratoma.

Complications. (1) *Hernia.*—The most common complication, estimated as occurring in from 60 to 70 per cent., and in Coley's series, 100 per cent., as he was able to demonstrate the hernial sac in every instance. Gibbons found hernia in 24 of his 27 cases. Strangulated or obstructed hernia demands immediate operation.

2. *Torsion of Spermatic Cord.*—Thorek reports a case in a boy, 15 years of age, with undescended testis, in whom the diagnosis of strangulated hernia was made. He collected a series of 22 cases in which the diagnosis was of strangulated hernia or the symptoms pointed strongly

to strangulated hernia. Eleven of the 24 cases traced in the literature occurred under the age of 16 years, the youngest in an infant. He states, in a review of the literature, that 47 per cent. of the cases of torsion of the spermatic cord occurred in ectopic testis.

Doolin makes the statement that there is no instance on record, to his knowledge, where torsion or strangulation occurs in the normally located testis, maintaining that it always occurs in ectopic testis.

3. *Inflammation due to traumatism* because of the exposed location of the organ is more frequent and often more severe because of the non-elastic structures in which the organ is situated.

4. *Malignant disease* in children is probably not much more common in this variety than in the normally located testis. In the 65 cases of malignancy Doolin reported it is not stated that any were among children, but that 75 per cent. were between 25 and 45 years of age. Koper found that 71 per cent. of the cases occurred after the twentieth year.

Doolin says that the undescended testicle is more liable to undergo malignancy.

Ecckles in his monograph states that of 38 cases of sarcoma of the testicle, only one occurred in an incompletely descended testis. Against this are the reports collectively by Hawar, Odiorne and Simmons, Schädel, and Hinman, who together report 248 cases of malignancy in testicles, 39 of which, or practically 12 per cent., occurred in undescended testis. Gibbons does not believe that malignancy occurs more frequently than in normal testis, but Le Conte in discussing Gibbons' article takes issue with him on this point, stating that at the Massachusetts General Hospital 54 cases of malignancy of the testis had been observed during a period of 26 years, and that six of the 54 were in undescended testis. He further quotes Schädel, who states that of 41 cases of malignancy in testes seen in a London Hospital in one year, 5 were in undescended testes. He states, however, that malignancy in childhood is uncommon before the twentieth year.

Symptomatology and Diagnosis.—In uncomplicated undescended testis in children no subjective symptoms may appear, but pain will be complained of in a certain percentage, as numerous cases have been reported in which pain was the one symptom that caused the child to consult the surgeon.

Nervous phenomena rarely developed prior to the age of puberty.

Strangulated hernia and torsion of the cord are two conditions that demand prompt recognition and surgical treatment. The symptomatology of the two conditions are often confounded, cases being diagnosed as strangulated hernia in which it was found to be torsion of the cord or testis, and *vice versa*, the diagnosis being made of torsion of the spermatic cord while operation revealed a strangulated hernia.

The objective symptoms are absence of the testis in its normal location, and finding the organ in an abnormal position; if the descent has not proceeded beyond the internal abdominal ring, the diagnosis will be problematic.

Treatment.—The treatment is principally operative to bring the ectopic organ into its normal location, but in view of Coley's statistics and in absence of complications, palliative measures, such as massage and gently pushing or pulling the organ down, may be followed for some time especially if progress appears to be made.

That the gland should never be sacrificed needlessly seems to be the opinion of the vast majority of surgeons. It is generally conceded, however, that the glands are usually useless so far as reproduction is concerned, although the internal secretions which control skeletal development, virility, and the sex characteristics are still present in the majority of cases of undescended testis. The time of operation or age at which operation should be performed should be not later than puberty, according to the views of all surgeons. Mixter states that the operation may be performed any time after three years of age, but if beginning atrophy from pressure should be noted, operation should be early. Keyes and MacKenzie think operation should be performed shortly before puberty; if there are no attending complications operation should be performed earlier. Cumston prefers the fifth or sixth year, but may operate any time after the fourth year, operation should be performed prior to puberty.

The operation of choice is the Bevan or modified Bevan operation—careful preservation of the blood supply to bathe the vas and the spermatic cord. In support of the necessity of preserving both the vessels of the vas and the cord I quote Mixter, who reports 30 operations on 23 patients for undescended testis, seven being bilateral, the ages ranging from 10 months to 12 years, one, 20 months, 10 from two to six years, 12 from 6 to 12 years, and who gives the late results in 26 operations. Two cases in which atrophy was present at time of operation did not improve in development. Eight cases showed atrophy and in all these cases partial or complete ligation of the spermatic vessels was done at the time of operation. Of 15 cases in which there had been no disturbance of the spermatic circulation, 14 cases were reported in which there was no atrophy; in one case there was no report. Of five cases in which there was partial disturbance of the spermatic circulation, reports were obtained in four and in all marked atrophy occurred after operation. Of nine cases of complete division of spermatic vessels, reports were obtained in seven and all showed marked post-operative atrophy. There were four cases of bilateral ectopic testis in which partial or complete severance of the spermatic vessels was necessary on one side but not on the other. Three reports showed that in each case in which partial or complete division was necessary marked post-operative atrophy appeared on that side, but on the side in which no vessels were severed there was normal development.

He states, and his figures would seem to substantiate the statement, that the results depend principally on the retention of all vessels both of the spermatic cord and the vas, and that this can be accomplished by careful dissection in practically all cases, using gauze and the finger.

The Bevan Operation.—An incision is made in the groin over the inguinal canal about 3 in. long. This cut should divide the skin, superficial fascia and the aponeurosis of the external oblique. Under the external oblique will be found a pouch of peritoneum extending from the abdominal peritoneum through the canal down to the scrotum. Often this pouch extends to the bottom of the scrotum even in cases in which the testicle has never been out of the abdominal cavity. It is covered by the cremasteric muscle and fascia and the transversalis fascia. These thin layers should be divided and the peritoneal pouch opened. The vaginal process should be divided transversely well above the testicle. Care must be exercised not to injure the cord as the tissues are very thin and easily torn. The use of fine instruments is advised. After completing the transverse division, the upper end is closed with catgut ligature, as in tying off the hernial sac, and the lower end is closed with a purse-string suture, making a tunica vaginalis for the testis. Then, with a gauze sponge, the peritoneum is carefully wiped from the cord. As the wiping proceeds the cord will lengthen gradually until the testicle can be well brought down in the thigh. Tense fibrous bands are torn either with the fingers or by blunt dissection and the cord is freed, excepting the vas and vessels; even the spermatic artery and vein are to be sacrificed if necessary to obtain more length, as occurs in exceptional cases. A bed is prepared in the scrotum by blunt dissection, in it the testicle is now placed and a purse-string suture inserted within the neck of the scrotum. The success of the operation depends on the ability with which a sufficient length of the cord may be gained with retention of its blood supply, so that the testicle may lie well down in the scrotum without tension. The inguinal wound is closed as in the ordinary hernia operation without transplanting the cord, but allowing it to remain in its normal location.

Davidson* describes an operation in which the vas and spermatic cord are transplanted and made to emerge internal to the deep epigastric. The operation then proceeds as in the ordinary Bassini, with double ligation of the deep epigastric artery. The whole of the posterior wall of the inguinal canal is incised, from the internal ring to the pubic bone, the vas is separated from the peritoneum until the desired length is obtained, and the spermatic vessels are also freed from the peritoneum. The length of the vessels is gained by following the long side of a triangle instead of the two short sides of the triangle. The author claims that the blood, nerve and lymphatic supplies are retained. The incised posterior wall is repaired and the cord is made to emerge from the lower angle of the incision.

Hydrocele.—Definition.—An increase in the quantity of fluid in the serous sac which envelops the testicle and epididymis (normally only a few drops of fluid) is termed hydrocele. Hofmakl† gives the following classifications:

* Surg., Gynec. and Obst., xii (1911).

† Hofmakl, Quoted by Pfaundler and Schlossmann.

A B

FIG. 190.—*A*, Communicating hydrocele. *B*, Hydrocele of cord—extravaginal. (Schultze, in Bruning and Schwalbe.)

A B

FIG. 191.—*A*, Hydrocele of spermatic cord with open vaginal process. (Schultze, in Bruning and Schwalbe.) *B*, Bilocular hydrocele. Processus vaginal is closed. (Schultze, in Bruning and Schwalbe.)

Congenital or Acquired.—(1) Hydrocele vaginalis testis et spermatici (congenital).

2. Hydrocele vaginalis funiculi spermatici communicans (congenital and acquired).

3. Hydrocele in combination with hernia (hydrocele hermosa).

4. Hydrocele vaginalis funiculi spermatici uni et multilocularis (non-communicating).

5. Hydrocele vaginalis testis simplex.

6. The bilocular form of Kocher, of which the location is in the distended extremity of the vaginal sac, partly in the peritoneum, partly in front of the external crural ring.

FIG. 192.—Hydrocele, complicated by hernia. (Kocher.)

FIG. 193.—Photograph of hydrocele of testis in a child of six weeks. (Testicle and epididymis are located upper posterior part of scrotum.) (Schultze, in Brüning and Schwalbe.)

There are two varieties of hydrocele, acute and chronic. The acute variety is a temporary collection of fluid, usually of no importance, following mild trauma or mild inflammation. There is a variety of chronic hydrocele found in children, which may be classified as follows:

1. *Communicating Congenital Hydrocele.*—The peritoneal sac carried with the testis in its normal descent has not been obliterated at the abdominal opening, but remains an open sac communicating with the abdominal cavity. It may communicate either freely or through a very small opening.

2. *Communicating Funicular Hydrocele.*—In this variety the abdominal portion is still patent but the lower or testicular end is obliterated, that is, the testicle is not in the hydrocele proper. It is possible to have one hydrocele superimposed on another in this variety by obliteration of the sac at different levels.

3. *Infantile Hydrocele.*—There is an obliteration or closing of the abdominal opening, with a collection of fluid in the funicular process and the common sac of the tunica vaginalis, making it irreducible, with fluid encapsulated in the scrotum.

4. *Hydrocele of the Cord.*—This is often mistaken for an inguinal hernia and in it a hernia may exist in which the sac is obliterated from the testicle upward to some level along the cord.

5. *Encysted Hydrocele of the Cord.*—Here both the peritoneal and scrotal ends of the sac are obliterated, with accumulation of fluid between the two points, usually at or near the external or abdominal ring. This is also mistaken for inguinal hernia.

FIG. 194.—Different forms of hydroceles. Coexisting herniæ in *b* and *c*. *a*, Simple hydrocele, *b*, multilocular with hernia, *c*, infantile hydrocele and hernia. (Pfaundler and Schlossmann.)

6. The *ordinary type* found in adults in which the accumulation is in the tunica vaginalis immediately surrounding the testis.

Etiology.—Congenital syphilis is probably the most frequent cause of hydrocele in infants. Vagilo in an analysis of 55 cases of hydrocele in infants under one year found that in 24 cases there was direct evidence of congenital lues; in five it could not be excluded with certainty, there being direct evidence in 40 per cent. In 115 cases of congenital syphilis 20 cases of hydrocele were noted.

Kocher, Cohnheim, Birch and Hirschfeld consider the hydrocele as the product of inflammatory irritation of the membrane of the testicle or of the spermatic cord. Kocher, therefore, proposed the term chronic serous periorchitis or chronic serous perispermatitis. Intrauterine inflammation of the testicle and spermatic cord is considered by some writers as responsible for the congenital form.

Tumors may be a cause of hydrocele. Traumatism is an etiologic factor. An inflammatory condition is always present.

Symptoms.—These are the same as in adults.

Diagnosis.—The diagnosis is usually made with greater ease than in adults owing to the thinness and transparency of the tissues. The differential diagnosis lies between (1) hernia, intestinal or omental; (2) tumors, solid and cystic; (3) inflammatory conditions; (4) hematocele; (5) syphilis; (6) tuberculosis of the epididymis and testicle.

In hernia there is an impulse on coughing; light is not transmitted. Hernia may be reduced readily and reappears promptly on standing or straining. Hydrocele when reducible is much more slowly reduced and reappears slowly on assuming the standing posture.

In tumor the light is not transmitted. Solid tumors have a more solid touch and are not elastic. In cystic tumors the light is not transmitted readily.

In inflammatory conditions the history and onset aid in making the diagnosis. There is pain on examination, possibly redness, heat, etc. There is a doughy sensation to touch and light is not transmitted.

In hematocele there is a history of recent injury and light is poorly transmitted.

In differentiating between the various types of hydrocele the following points should be borne in mind:

1. In communicating congenital hydrocele swelling usually exists from the right inguinal ring to the lower portion of the scrotum, the testicle being usually posterior and fairly high, or just within the scrotum. If the communicating opening is large the fluid within flows back spontaneously into the peritoneal cavity if the patient lies on his back; if the opening is pinpoint, considerable pressure must often be used in order to cause the fluid to pass into the peritoneal cavity. Hernia is often combined with this form of hydrocele; in fact, this type of hydrocele may often be mistaken for hernia. In hernia in the course of reduction a gurgling and sudden emptying of the cavity usually occurs. Hydrocele is dull on percussion, translucent, and slightly fluctuating.

2. In communicating hydrocele of the cord the elongated, rather elastic swelling about the scrotum is reducible, as in the communicating congenital hydrocele.

3. In ordinary infantile hydrocele the fluid forms a rather oval, elastic, rather tense, and apparently fluctuating and translucent collection of fluid; as a rule the condition can readily be made out. Containing the ring, it naturally cannot be reduced with pressure or by position and there is *no* impulse on coughing.

4. Encysted hydrocele of the cord varies in size, is usually spindle-shaped or at least elongated, and may appear firm. On account of location light cannot be transmitted and lymphatic gland or neoplasm may be thought of. Naturally when the testis is situated in the scrotum, irreducible hernia may also have to be considered. If the mass is larger the findings may be more positive and the diagnosis made with certainty.

Treatment.—Depends on etiologic basis. In congenital lues the treatment of the syphilitic condition with mercury and iodid will in the majority of the cases effect a cure.

In the tuberculous variety the appropriate treatment for this condition should be given.

Expectant treatment is justified because in the course of weeks and months spontaneous recession occurs in many cases. If this does not take place, aspiration may be tried.

Simple aspiration will suffice in many cases and, plus systematic massage, will in the majority effect a cure.

Irritants should never be injected following aspiration in any of the forms of hydrocele that communicate with the peritoneal cavity, as the irritant substance will easily find its way into the peritoneal cavity, thereby causing peritonitis and severe adhesions. My personal observations do not agree with the good results claimed by various authors who state that simple aspiration and ordinary treatment suffice. If puncturing, application of heat and support are not sufficient, operative interference is indicated. In both the communicating congenital hydrocele and hydrocele of the cord operation is obligatory. Operations for encysted hydrocele of the cord are desirable at an early period as age conditions undoubtedly pre-dispose to hernias.

The operative procedure of resecting the tunica (Jaboulay's operation) or the Andrews' bottle operation in the ordinary types may be followed in cases that do not respond to palliative measures. Nicoll describes an operation in which the incision is made in the groin down to the cord, the hydrocele with the testis being then pushed up into the incision. The sac is aspirated when the sac and testis are pulled out and the sac is treated by resection and stitched to the everted edges back of the testis, after which it is returned to the scrotum and the incision closed.

Andrews' Bottle Operation.—The scrotum is made tense by grasping it with the left hand. An incision is made through the scrotum and various layers of areolar fascia down to the tunica, all the layers being carefully dissected from the tunica, this being delivered through the external incision. After careful dissection and having freed all the layers excepting the innermost layer of the tunica vaginalis, this is punctured high up and the testicle is inverted through the incision and the inverted tunica is reflected along the epididymis and cord, where it may be fastened by a single catgut suture; if the opening has been made small this is not necessary. The opening in the tunica vaginalis should only be large enough to squeeze the testicle through. The external incision is closed with horsehair or silkworm-gut without drainage.

Hematocele.—Hematocele is of very rare occurrence, but has been encountered in several instances of breech presentation, undoubtedly due to injury and traumatisms of any kind to the scrotal region, which may be productive of an accumulation of blood in the

cavity of the tunica vaginalis. Of course, blood may enter this sac when diseases of the epididymis or testis are present; in which case it is simply an intercurrent condition.

Puerperal Hematoma.—This is due to compression of the root of the scrotum in the course of labor in a breech presentation. Such a case was reported by W. G. Spencer.* The tumor was an enormous sanguinary mass produced by rupture of the spermatic veins.

Tumors.—Tumors of the male genitalia are rare in infancy. Of the 19 cases collected by Steffen, six involved the prostate and 13 the testicle. Quoting Pfaundler and Schlossman:

"**Cancerous degeneration of the prostate** has hitherto been observed only in children up to eight years of age. The youngest was six months old. The tumor is generally a medullary one. It may attain considerable size and may produce symptoms due to displacement of the pelvic organs. Metastases have been found in almost all the internal organs. Pain and difficulty on urination are the earliest symptoms. A point of importance from the standpoint of diagnosis is that the neighboring inguinal glands are early involved. The general health soon suffers. The diagnosis is established by palpation through the rectum. The fatal termination, which as a rule occurs in from three to seven months, cannot be averted even by operative interference.

"**Cancer of the testicle** is somewhat more frequent than cancer of the prostate and attacks by preference the very youngest children, often during the first few months of life. The youngest case was in a child only six weeks old. Medullary carcinoma and the scirrhus form have been described. The former is of more rapid growth and more malignant."

At onset cancer of the testicle is not accompanied by any symptoms. It seldom causes pain. As it increases in size it causes discomfort by its weight. The general health is notably impaired and a decided cachexia appears.

W. B. Coley† reports a case of embryonal carcinoma of the testis in an infant. The tumor was removed and in three weeks recurred. It was again removed, but recurred. It was removed a third time. Following the removal the patient was given injections of mixed toxins of bacillus erysipelas and prodigiosus. When the case was reported, seven months later, there was no evidence of recurrence.

Prognosis is unfavorable because of the great tendency to metastasis. Only an early operation can promise hope of cure.

Sarcoma.—A difference of opinion exists regarding the relative frequency of sarcoma and carcinoma. Ewing‡ states that this formerly extensive group of tumors has been narrowed by the elimination of many cases of carcinomata, which were formerly recognized or regarded as alveolar sarcoma. A great number of other authors consider sarcoma the more frequent.

* Path. Soc. Jour. (1892).
† Southern Surg. Tr., xxx.
‡ Surg., Gynec. and Obstet. (1911).

Ewing, in the article mentioned, classifies tumors of the testis as follows:

Fibroma.—Pure fibroma are rare, the two cases collected by Curling being among the few collected in older literature.

Chondroma.—Pure chondroma very rare. Most of the cases reported are cystic.

Myxoma.—Kocher and Langhans could find no case of pure myxoma.

Lipoma.—Wilms considers it doubtful if any pure lipomata of the testis have been observed.

Myoma.—No evidence of pure myomata of the testis, but a one-sided development of a teratoma.

Rhabdomyoma.—Very rare indeed and if it does occur is of slight clinic importance.

Adenoma.—Existence of pure adenoma has been demonstrated. Two cases only have been observed, both in undescended testis.

Sarcoma.—This formerly extensive group of tumors has been narrowed by the elimination of many cases of carcinomata, which were once recognized or regarded as alveolar sarcomata carcinomata.

Lymphadenoma and Lymphosarcoma.—Distinguished by involvement usually of both testes, rapid development, and by the development of multiple metastases in the skin.

Spindle-cell Sarcoma.—Not sure of pure entity. There may be tumors composed chiefly of spindle cells but their entire freedom from other elements has not yet been determined.

Ewing reports a case of lymphosarcoma, primary in the rete testis, in a child 5½ years of age, with metastases in the skin, inguinal and abdominal lymph-nodes, liver and kidneys. Duration was twelve weeks.

Teratomata and Dermoid Cysts.—These are congenital growths, the dermoid cyst containing embryonal material as skin, bones, hair, teeth, cartilage, etc., and even gray matter of the brain, while the teratomata constitute mixed forms of tumors containing congenital remnants of blastodermic tissue, chorio-epithelium, as their distinguishing characteristics. In general they present the features of carcinoma or sarcoma or of mixed tumors generally, and are decidedly malignant. Their early recognition and removal is of greatest importance. Dermoid cysts of the testis may be incorporated within the gland or they may displace it to one side, causing pressure atrophy, or they may prevent development of the testis. The tumor may delay or prevent the proper descent of the testis. It may, however, develop in the scrotal wall and subsequently become connected with the testis.

These tumors, while congenital, may be so small as to attract no attention until the period of puberty, when increased growth and activity bring them into prominence.

Diagnosis is usually not difficult. In certain cases an exploratory incision may be necessary or puncture with a fine needle may reveal bone or teeth or these may be felt with a probe passed through a

fistula. Their congenital origin is of the greatest importance in diagnosis.

Treatment.—Removal of the tumor is the only treatment recommended and whenever possible should be done with as little interference with the testicle as possible.

Tumors of the Cord.—Malignant growths of the testicle may extend upward into the inguinal canal and involve the spermatic cord. Primary involvement of the cord by different types of tumors is exceedingly rare.

Syphilis of the Testicle.—That the testicles are frequently involved in congenital syphilis seems an established fact. The first case of syphilitic orchiepididymitis reported was by Gosselin in 1858, and since then many cases have been reported. Hutinel states that one-third of the congenitally syphilitic male children show changes in the testicle. However, a large percentage it would seem would show changes only on microscopic examination.

The condition seems to be an interstitial inflammation with formation of fibrous tissue about the seminal tubules, as gumma are rarely reported.

The increase in size of the testicle is often insignificant, seldom reaching the size of an adult testis, but on careful examination the organ is more resistant, that is, the tension is increased.

The period of onset is most frequently noted as within the ages of four months to two years, rarely first noted at puberty and may be manifested at birth.

Twenty-five per cent. are accompanied by hydrocele, and a considerable number are bilateral.

Carpentier makes the following summary in his article on affections of the testicle in hereditary syphilis:

1. The involvement may be so slight that microscopic examination is necessary to detect.

2. A small percentage may be detected by physical examination and as a general rule the process is noted from birth up to two or three years of age, not often after three years of age and rarely at puberty.

3. The testis proper is more often alone involved. The epididymis may be involved with the testis, but rarely the epididymis alone is involved.

4. Frequently the condition is bilateral.

5. Hydrocele is frequently associated, and often the one thing that leads one to suspect syphilis in the young infant.

6. Hydrocele of the cord is often found in congenital syphilis.

7. The swelling of the testis is painless and may or may not be nodular—usually not.

8. The enlargement of the testis is not great—very rare that it reaches the size of a small egg. Frequently no enlargement but increased tension.

9. On microscopical examination the majority show simple interstitial inflammation. Gumma is rare.

10. Impotence and sterility often follow in cases untreated and a certain number of atrophic testes may be traced to hereditary lues.

Taylor discusses six cases, the ages ranging from three months to 2½ years, and one of 15 years. Two cases showed involvement of the epididymis and in one of these the testicle was studded with nodules. In three there was involvement of both testes and in three the disease was unilateral. In one case the testicle atrophied at the end of six months' treatment, and in one case there was abscess formation.

Diagnosis.—Usually other signs of hereditary syphilis are present. The differential diagnosis lies between new growths, tuberculosis, and syphilis.

In new growths of a malignant type the growth is more rapid, with glandular involvement and possibly metastases. The new growths will not respond to luetic treatment.

In tuberculosis there may be an involvement of the seminal vesicles, prostate and vas. The epididymis is always involved, while in the majority of cases of syphilis it is not. The von Pirquet test is positive.

I have been unable to find the involvement of the seminal vesicles and prostate in congenital lues, and the involvement of the cord is very rare.

Treatment.—Antiluetic treatment—inunctions of mercurial unguentum together with the iodids in the form of the syrup of the iodid of iron; general hygienic care, fresh air, sunshine, and nourishing diet.

Congenital Atresia of the Urethra.—Closely allied to and in etiologic connection with the malformations of the urethra are the atresias of the canal. Besides the very rare complete absence of the urethra and penis or the total absence of the urethra with the presence of the penis there may be:

1. Closure of the External Urethral Orifice by Membranous Adhesions or Growth.—The cellular layer, which normally cements the glans and the prepuce, may produce it by an overgrowth over the meatus.

2. Imperforatio Glandis.—There may be only a shallow groove at the normal site of the meatus or there may be no vestige of an orifice.

3. More Extensive Atresia of the Urethra.—Through primary defect in development poor development of the urethra may take place or there may be secondary obliteration by epithelial growth and cementing of the opposing surfaces. The entire urethra may be missing or there may be atresia of only a part, for example; the middle portion may be closed or absent with the anterior or posterior portion open.

Symptoms.—The symptoms are those of retention of urine. These may occur intra-uterine with great distention of the bladder and may lead to reopening of the urachus with formation of an umbilical fistula and may cause dystocia. If the child is born alive, the failure to void urine is soon discovered. The mere adhesion of the external meatus is frequently overcome by the pressure of the urine and so is

spontaneously cured. In other cases there may be a globular protrusion, easily discovered. In all other cases the straining efforts, restlessness of the child, the distention of the abdomen, and frequently a considerable distention of the urethra itself behind the obstruction are readily discovered.

Treatment.—In the membranous cases a mere perforation suffices. In other cases operative interference on a larger scale is necessitated. To find the posterior end of the urethra with trocar and pointed bistouries is dangerous, though it has been successful in some cases. External urethrotomy and attempting to reach the urethra through this route is more safe and more easily done. Only in atresia of the glandular urethra with distention behind the glans is perforation of the glans justifiable. Mere puncture of the bladder with a trocar (paracentesis) may be resorted to as a palliative measure.

Congenital Narrowing of the Urethra.—Most common is a narrowing of the external urethral orifice, which may be pronounced and lead to considerable difficulty in urination. Repeated sounding will usually remedy this matter. It may be necessary to do a meatotomy or more extensive slitting of the contracted portion.

Real cylindrical strictures are very rarely congenital, but cases have been reported by various authors. Other cases unquestionably have been acquired in the first years of life. The author has found one case of fibrous stricture of the bulbo-membranous urethra in a boy 11 months old, unquestionably congenital in origin. Besides the congenital folds of the fossa navicularis and the type of stricture above mentioned near the end of the urethra, strictures also occur between the fossa bulbosa and membranaciæ and in the pars prostatica, or the narrowing may be due to halfmoon-shaped folds causing narrowing of the lumen with obstructive symptoms.

Since the use of the cystoscope it has been observed that there are folds that lie chiefly on the floor of the bladder at the junction with the urethra, even extending into the prostatic urethra, that play a part in the obstruction shown in a child by inability to urinate, difficulty of urination sometimes causing acute retention. These folds have only been recognized since cystoscopy has been practiced. Unfortunately this method of examination has not been employed in children as frequently as it should be, hence, the cause of urinary difficulties has been frequently overlooked and only when patients reach adult age and urinary symptoms occur, are these conditions recognized. Dividing the fold or even removing a V-shaped piece has been carried out without satisfactory results. I have had occasion to practically dissect these folds, even those reaching into the prostatic urethra, and I believe this procedure gives more permanent relief. Previous to cystoscopy these conditions were not uncommonly discovered on the operating table.

Symptoms.—The symptoms in these cases usually develop comparatively late and frequently only when infection is added. Posence reports a case in an 11 year old boy in which a scarlet fever cystitis

was followed by urethritis with which the symptoms of stricture appeared. These rapidly subsided under treatment with bougies and

FIG. 195.—Hypospadias in young boy (seen from below). Note apron shaped prepuce with urethral furrow in glans. *a*, Spurious opening or furrow in glans, *b*, existing opening. (Schultze, in Brüning and Schwalbe.)

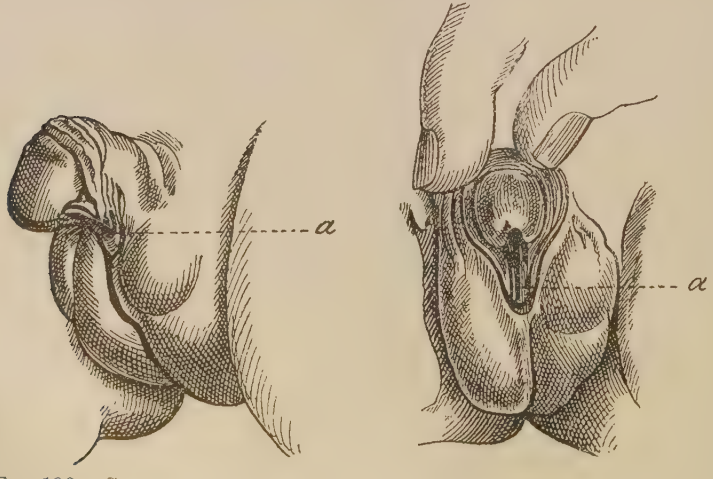

FIG. 196.—Scrotal hypospadias showing (*a*) true urethra. (Karewski.)

bladder irrigations. Other cases of similar character are reported in the literature.

Hypospadias.—Hypospadias is a congenital malformation in which the urine escapes through an abnormal opening at a variable distance from the tip of the glans on the lower surface of the penis

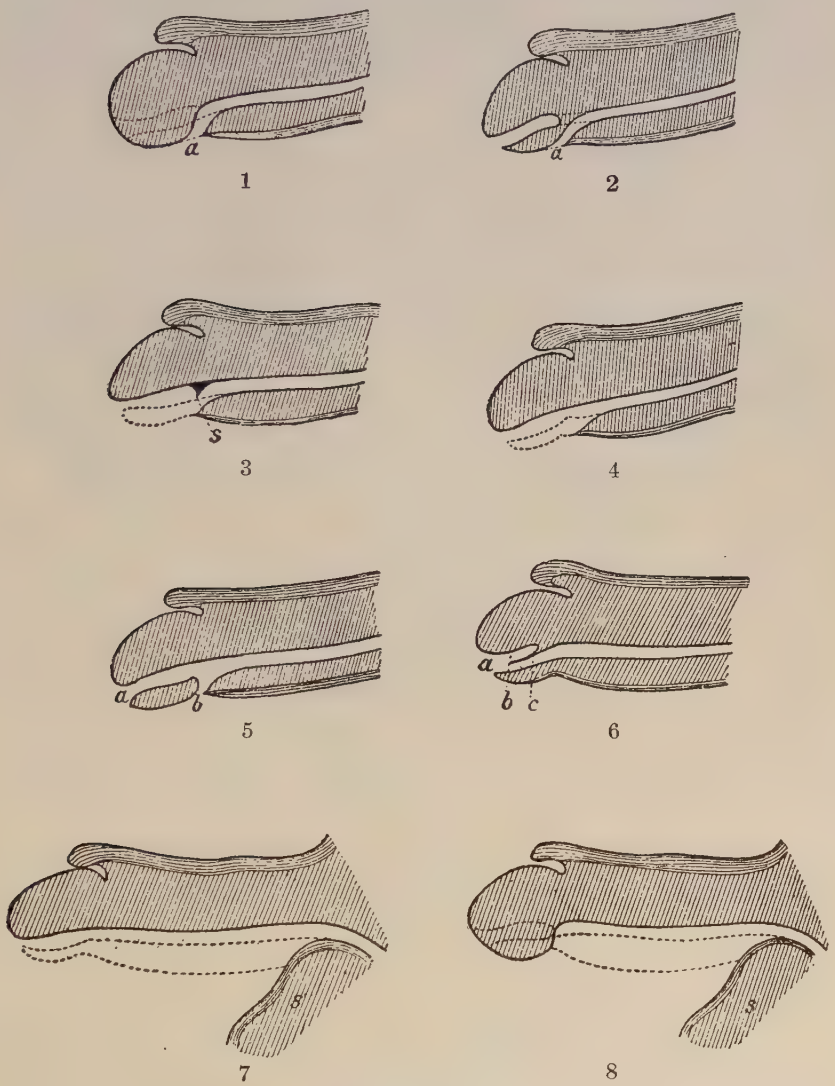

Fig. 197.—Schematic drawings showing varying degrees of hypospadias. (Karewski.)

instead of from the normal point at the extremity of the glans. According to some authors, as Burkhardt, this anomaly is the most common of all deformities of the urethra and according to different authors occurs once in every 300 to 350 persons. F. E. Brown declares it to be the

most frequent deformity of the entire body. Three forms are distinguished by most authorities:

1. Hypospadias Glandis (Balanic or Glandular).—This is the most common form. Here the opening is abnormally located in the glans or just behind it in the neighborhood of the frenum, which at times may be absent. The glans shows a more or less deep, longitudinal furrow. Other abnormalities which may co-exist are:

(*a*) A completely split glans.
(*b*) In place of the balanic furrow there may be a fistulous tract with the opening at the normal site of the glans.
(*c*) Torsion of the penis.
(*d*) Deviation of the raphe from the median line.
(*e*) Rudimentary penis.

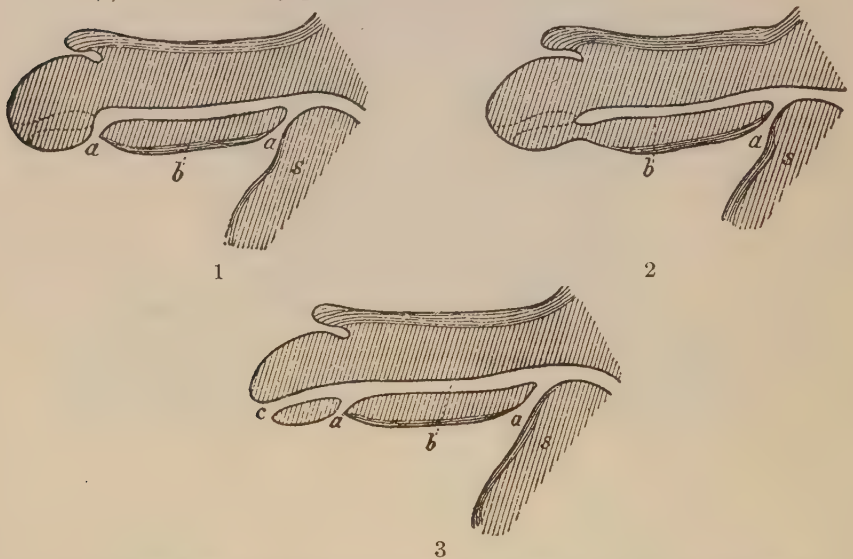

FIG. 198.—Schematic drawings of hypospadias—sagittal sections. (Karewski.)

2. Hypospadias of the Body of the Penis.—In this type the opening is somewhere on the shaft of the organ between the glans and the penoscrotal fold. This form is much rarer than the first variety. Associated anomalies may be similar and usually more pronounced than with hypospadias glandis.

3. Hypospadias Perinealis et Scrotalis.—This form is most rarely found. In this the opening is located between the penoscrotal fold and the perineum, the scrotum being split and the urinary opening found in the depths of the furrow in the shape of a slit 3 or 4 cm. in front of the anus. A rudimentary and imperforate penis is quite commonly present.

Three additional grades are recognized by some authors, notably, F. I. Brown, Morrow's System: Mixed types (1) glandulopenile; (2) penoscrotal; (3) perineoscrotal.

Etiology.—The causes of hypospadias are obscure. It has been found in several members of the same family. It is considered the result of failure of the lateral halves of the penis to unite in the median line, an abnormal development and faulty union of the three embryologic segments of the urethra. But the developmental theory does not explain all cases. In certain cases there seems to be no doubt that rupture of the urethra has occurred during fetal life.

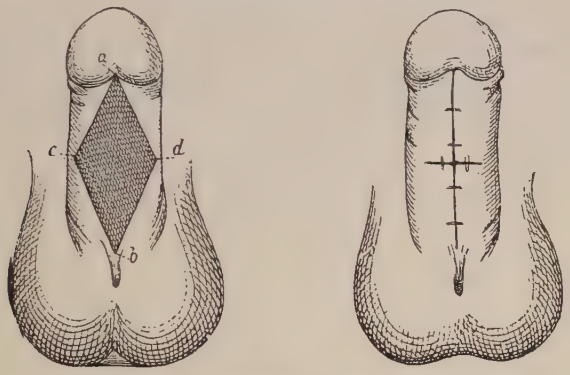

Fig. 199.—Plastic operation for hypospadias according to Duplay. (Karewski.)

Symptoms.—In mild cases no symptoms are shown besides the obvious deformity. In the more extreme cases symptoms referable to disturbances of function occur. Disturbances of urination are very common in the extreme types and consist in dribbling, scattered stream causing soiling of the garments and resulting in excoriation of the parts, eczema, and frequently a persistent urinous odor. In balanic and penile hypospadias copulation is not necessarily interfered with, though fecundation may be hindered. The rudimentary penis, down-

Fig. 200.—Incisions in glans by Duplay for plastic external urethral orifice in hypospadias. (Karewski.)

ward curve and adhesions to the scrotum usually render coitus impossible in the perineal type.

Diagnosis.—The diagnosis is usually easy and mere inspection suffices, but in the newborn there may be a question of sex, as undescended testicle may be associated with the anomaly. The scrotal halves may look like the labia and the adherent rudimentary penis like a clitoris. Abdominal palpation combined with rectal examination may reveal the existence of uterus or prostate.

Prognosis.—The prognosis varies with the severity of the condition and the age of the patient.

Treatment.—The author has failed to describe the various operations for Hypospadias and would refer the reader to any standard textbook on surgery where many pages are given to this wonderful subject.

Epispadias.—Epispadias is a congenital malformation consisting of a more or less extensive division of the upper wall of the urethra, the corpora cavernosi being separated and the urine escaping through the gutter-like cleft on the dorsum. This deformity is quite rare as compared with hypospadias. It is found most commonly associated with incomplete closure of the anterior wall of the bladder (exstrophy). Epispadias may occur without exstrophy, but the reverse condition is never found. Other congenital deformities, as imperforate meatus, absence of prostate and fistula of the urachus, pubic fissure and distorted penis, may co-exist.

Three distinct types of epispadias are usually distinguished:

1. Complete Epispadias.—This is the commonest form, involving the deeper urethra, and occurs in conjunction with ectopia vesicæ, the whole urethra being open as far as the bladder.

2. Glandular Epispadias.—This form is extremely rare, the opening lying above and behind the glans. Two types have been described. The glans may be merely furrowed on its upper surface by a shallow urethral trough, or more rarely the entire body of the glans may be divided into two halves, being united only by the floor of the urethra at their lower margins. The prepuce never seems to be involved.

3. Epispadias of the Penis.—Here the opening lies between the glans and the symphysis and most commonly immediately in front of the symphysis. The penis in this type is usually rudimentary, usually curved upward and almost always twisted. Usually the penis is drawn in and in contact with the protruding abdominal skin which continues usually into the scrotum. The frenum is well developed and the prepuce is massive and hangs in folds over the well-developed scrotum. The true relations are best seen by pulling the glans downward and forward. The urethra is seen upon the dorsum, gutter-like, a furrow beginning at the glans and running to the root of the penis. This groove may extend to the apex of the glans or may end at some point behind it. The glans may be uninvolved and solid. The mucosa of the urethra, which is broad and spread out, shows all its usual characteristics and the urethral lacunæ are distinctly seen. The edges of the furrow are rounded, gradually merging into the surrounding skin. Just in front of the symphysis the urethral groove terminates in a funnel-shaped opening formed in part by a fold of overhanging abdominal skin. The symphysis pubis is usually absent and the rami of the pubes are distinctly separated. Between their ends is found a depression in which rests the glans penis.

Symptoms.—Besides the physical findings above described, the symptoms are almost exclusively of a functional type. Incontinence, though not always present, is the rule. When epispadias is incomplete this symptom is lacking or may be slight. The stream is divided and scattering even in patients who have otherwise fairly good control of

the urinary act. The clothing is soiled and the wetting of surrounding parts leads to excoriations. A small bladder with deficient muscular control may be present and the patient will be unable to hold the urine when standing. The sexual function of the penis is fairly good and erection and ejaculation occur but copulation is imperfect and sterility is the rule, due to inability to ejaculate into the vagina.

Treatment.—As far as the treatment is concerned, which is entirely surgical, it will be necessary to refer to the standard surgical textbooks. In cases of epispadias as well as in all the hypospadias cases except of the first degree each case will have to be studied individually and the most suitable operation selected. For the balanic type the Beck operation has been in recent years the favorite one. It has been my experience, however, that this operation does not fulfill the requirements. A true plastic operation that will prevent distortion at the time of erection is the operation which unquestionably gives a more satisfactory result.

Phimosis.—This is one of the most important anomalies of the penis. It consists in the abnormal contraction of the preputial opening to such an extent as frequently to render retraction entirely impossible. The condition is practically always congenital. Acquired cases, due to inflammation and edema of the prepuce, are usually of temporary duration only. The opening in the prepuce may be of pin head size or in the incomplete variety part of the glans is found exposed. The prepuce in the complete variety is either short and the edges of the orifice thin, or it may be from 1 to 4 cm. long, hanging in front of the glans, the preputial orifice being in front of the meatus or deviating from below upward (epispadial prepuce). A short frenum and strictured meatus is frequently associated. Phimosis is extremely frequent and usually exists in some degree at birth, commonly disappearing in six or seven years or at puberty. If it does persist a hard, sclerous ring is usually formed. Adhesions may be combined with phimosis but it is also common to find simple elongation (redundant prepuce) unattended by phimosis.

Symptoms.—Phimosis may simply prevent retraction of the foreskin or the contracted orifice may be so high as to obstruct the flow of urine, causing more or less pronounced disturbances of urination. If the meatus is very small and especially if the opening is not parallel with the urinary meatus, stagnation of the urine beneath the prepuce is common and there may be distinct ballooning at every act of urination if no adhesions are present, causing, according to Leguen and Virchow, a veritable preputial bladder. Straining in these extreme cases is common and the urine may flow in drops or in only a thread-like stream. Hernia or rectal prolapse may be produced and hydronephrosis, pyelitis, and pyonephrosis have even been attributed to phimosis by some authors. In ordinary cases urination is not difficult but posthitis and balanitis with resulting dysuria due to inflammatory swelling are more common and are directly attributable to the inability to keep the mucous membrane clean. The constant irrita-

tion may lead to inordinate excitability of the organ and masturbation. Nocturnal urinary incontinence may be due to reflex contraction of the bladder (vesical tenesmus), produced by irritation. Enuresis, convulsions, epilepsy, chorea and night terrors are attributed to phimosis in many instances. Preputial calculi, due to stagnation of urine behind the prepuce in the balanic cavity, may be formed, or very minute calculi, as formed in the kidneys or bladder, may become lodged here and become enlarged by continuous deposits, reaching at times enormous sizes. Many such cases are recorded in the literature. These calculi may give rise to sudden retention of urine or their presence may be manifested by symptoms of balanitis and even ulcerations may be produced. Even a pronounced degree of phimosis may be present and produce no symptoms at all or only a slight irritation.

Treatment.—A slight degree of phimosis is present at birth and circumcision is perhaps too often performed, nor are adhesions between the prepuce and the glans an absolute abnormality nor one which time cannot correct. Every case of true phimosis should receive prompt attention to overcome the difficulty. Forcible retraction or stretching with an artery forceps may suffice in some cases or slitting of the preputial orifice may be performed. Much to be preferred, however, if any operative interference is necessary, is circumcision. The best time for treatment is in early infancy, except in those cases in which dysuria exists, when treatment is best postponed until the umbilicus has healed or even for a month or two. It is not advisable to postpone operation until the boy runs about, as it is difficult to restrain him during the healing process and balanitis and infected prepuce will frequently then complicate matters.

Paraphimosis.—Paraphimosis is a condition in which the prepuce has been retracted behind the corona glandis and, owing to the constriction caused by its interference with the circulation in parts distal to it, cannot readily be replaced. This condition has been frequently referred to in the textbooks as Spanish collar. Edema, bluish discoloration, and even gangrene in the glans may develop in these cases. The condition frequently follows retraction by the mother or nurse in cleansing the organ or may be produced by the patient himself. If the foreskin is retracted by the nurse or mother, circulatory conditions causing swelling and edema of the glans are responsible for the inability to retract the glans. Apart from the appearance already noted there may be pain and dysuria. If unrelieved, sloughing and ulceration may sooner or later result. Considerable edema and later inflammation may be due to a constricting band caused by a prepuce which is not extremely tight.

Treatment.—A few moments of firm compression preceded by application of cold compresses to reduce the swelling may enable one to readily draw the foreskin forward to its normal position. Lubrication of the glans may be made with oil or vaseline and if the surgeon encircles the penis just behind the swelling with his left index finger and thumb while with the other hand he gently and persistently presses

the swollen glans backward with thumb and index finger, the prepuce being pulled forward, he can usually secure reduction in the more pronounced cases. If relief by this method is impossible, the constricting ring of skin must be divided by longitudinal incision in the mid-line of the dorsum of the organ, by inserting a blunt-pointed bistoury flat-wise beneath the constricture. Circumcision should be performed in every case of paraphimosis after the swollen tissues have returned to the normal state.

Adherent Prepuce.—Adhesions of the preputial lining and the glans is normally found in a great majority of newborn infants and these adhesions disappear in the early months of life only with the growth of the penis. These adhesions may, however, persist even for years, and must then be considered pathologic, the adhesions becoming firm and the condition giving rise to many of the symptoms of phimosis. Retention of smegma occurs and balanitis is frequent. Smegma usually collects in quantities behind the corona and priapism and painful urination together with balanitis may result, with decomposition of the secretion.

Treatment.—Prompt attention should be given to this condition. Forcible retraction in the newborn should be carried out, followed by careful cleansing and lubrication with sterile oil or vaseline. The foreskin is then drawn forward again. This retraction and washing should be carried out daily by the mother to prevent reformation of adhesions. Never should the glans be allowed to remain uncovered, as paraphimosis may result. If several months have elapsed since birth without this initial retraction, the adhesions may have become quite firm and separation with a probe or grooved director may be necessary. If allowed to remain it is sometimes impossible to find the line of cleavage between the adherent surfaces. I have seen many cases in adults in which the individuals have never seen the glans because of these adhesions. Occasionally adolescent individuals submit to operation and allow removal of the external layer of the foreskin. In operative procedure, because it is impossible to separate the agglutinated surfaces without making the surface of the glans raw, cicatricial tissue will result. Under the circumstances it is my opinion that in these cases the operation is best left undone, unless it is performed with extreme care.

Balanitis and Balanoposthitis.—Inflammation of that part of the balanopreputial membrane covering the glans is termed balanitis, while that of the portion covering the prepuce is called posthitis. Inflammation of the entire balanopreputial membrane is called balanoposthitis.

Predisposing factors are, a foreskin congenitally too long or too tight, a short frenulum or a badly fitting prepuce, and various subpreputial pathologic conditions, such as herpes, vegetations, chancroids or irritating discharges. The exciting causes are uncleanliness, allowing the accumulation and decomposition of smegma, either through carelessness or inability to cleanse the parts because of the presence of

phimosis or adhesions. Diabetes is another cause of balanitis, as well as incontinence and constant dribbling of urine due to cystitis, cerebrospinal diseases, etc.

Simple Balanitis.—The mucosa of the glans appears bright red, moist, spongy and swollen. Maceration and erosion of parts of the mucosa take place and deeper ulcerations may appear. The entire glans may become markedly swollen and edematous, especially around the corona glandis.

Balanoposthitis.—If posthitis co-exists a characteristic mattered, moth-eaten appearance is noticed due to the irregular, macerated epithelium, which in places is thrown off. Herpetic lesions are not infrequent on the glans and may lead to erosions as rupture occurs.

In the secondary cases of balanitis, those due to herpes, chancroids, chancre, or vegetations, unless phimosis or adhesions exist, the cause is readily detected by retraction of the prepuce. Copious discharge, marked edema, and redness are common in these cases.

Symptoms.—The symptoms accompanying these conditions are itching, and the sensation of heat, which are exaggerated through the handling of the parts by the patient, rubbing and pressure of the garments, etc.; burning and stinging pains are greatly increased during urination. The preputial opening may be covered by a thin, yellowish, sticky secretion, which may cause the glueing together of the meatus and the orifice of the prepuce. Retraction of the foreskin may cause considerable pain.

Balanoposthitis is a frequent complication of urethritis and is especially marked and occurs early in cases in which the foreskin is long and tight.

Treatment.—If the cause can be removed the simplest treatment frequently suffices to remedy matters. Neglect of this condition may lead to phlegmonous inflammation. Permanent thickening of the prepuce may result. In cases due to retained and decomposed smegma, repeated washing with warm water, and applying some dusting powder, followed by placing a thin film of absorbent cotton between the prepuce and glans, is usually sufficient. Application of lotio plumbi is preferred in some cases. After cleansing the parts it may be repeatedly applied on a thin film of cotton spread evenly over the glans. Eroded portions may be touched up lightly with a silver nitrate stick, this being preferable to the dilute solutions of silver nitrate which cause more pain to the child on account of the necessity of more frequent application. In cases of secondary balanitis the cause must be removed, for example, vegetations, chancroid, etc., by appropriate treatment. In cases of specific balanitis, calomel, or a solution of bichlorid of mercury 1:5000, on a film of cotton, should be applied after thorough cleansing of the parts. Antisyphilitic treatment is, of course, to be instituted at once. In cases of chronic balanoposthitis circumcision should be performed. Slitting of the prepuce in the dorsal aspect may suffice in some cases or it may be desirable to carry out a dorsal slitting as a preliminary or palliative

measure, for instance, in cases of pronounced inflammation or of chancroid.

Foreign Bodies of the Penis.—Injuries to the urethra may result by instrumentation through introduction of foreign bodies by the patient himself, or the lodging of a foreign body, such as catheters or bougies, in the urethra. Lodging of urethral calculi in their passage from the bladder is not uncommon. Numerous cases have been reported in the literature. These calculi, some of which may pass without causing severe trouble, may result only in a certain amount or irritation, while others, becoming impacted, cause symptoms ranging in severity from pronounced irritation, or may be the cause of acute retention, with later urinary infiltrations. An impacted calculus frequently leads to the formation of urethral diverticuli, which will be described in another section.

A case of infiltration due to calculus, in a boy 15 months old, is of interest in this connection. It was reported by Durand.* The mother noticed the urinary stream becoming thread-like. The next day there was swelling of the scrotum, penis and regio-suprapubica. On the following day the child passed a bean-sized stone, the shape of an egg. All the tissues were strongly infiltrated and there was edema in one spot of the scrotum, but no necrosis. After multiple incisions, rapid healing and spontaneous complete recovery followed.

Stones may become impacted in the urethra, distending its walls and causing gangrene.

Encircling Foreign Bodies of the Penis.—Bakas reports that hairs, threads, wire, rings, have been found to encircle the penis, occasionally applied in play or even for purposes of masturbation; again mothers have used compression, by string or other fabrics, to prevent wetting of the bed. Naturally the appearance varies from a simple edematous swelling to necrosis, depending on the time which has elapsed since their application. In many instances the patient is unable to pass urine. Cases have been reported in which necrosis has taken place and spontaneous perforation of the penis followed. In these instances, naturally, the encircling body is removed spontaneously. However, in most instances it must be removed, often under an anesthetic, and in case the offending body is a metallic ring, the work of removal is often tedious.

Urethral Calculi.—Englisch explains the great frequency of urethral calculi in the second year by the congenital narrowness of the urethra; in the eleventh to fifteenth year by the abundance of blood-vessels and the swelling which is associated with it.

Regarding stones incarcerated in the urethra, English states that more than one-third occurred in children; that most cases were observed in the second year and between the eleventh and fifteenth years.

Stones may become lodged in the urethra proper in their passage from the bladder or may produce diverticula or be formed within these pockets.

*Soc. d. Chir. (1898).

Geis-Dudenhofen reports a case of urethral calculi, 12 in number, all faceted, one behind the other. The patient claimed to have felt these for three years. Dysuria had persisted since early youth.

Preputial Cysts.—These cysts are usually located in the neighborhood of the frenulum, most often causing the inner leaf, sometimes the outer leaf, of the foreskin to bulge. They reach at times the size of an English walnut. The smaller ones, however, are much more common. They are usually found in the median raphe of the penis or even occasionally on the scrotum. As a rule, they are single, but occasionally are multiple and then are of varying size. They are tense and elastic in character, give rise to no disturbances and as a rule need no surgical interference. If of considerable size these cysts may be opened under surgical precautions. They are usually found to contain a clear fluid.

Fig. 201.—Preputial cyst in 10 months old infant. (Mucoid cyst.) (After Mermet.)

Tumors of the Penis.—The only tumors that have been reported and seen by the author are papillomata that appear about the external urethral orifice or protruding from the urethra. Burkhardt states that no previous gonorrheal infection is necessary, as is believed by some authors. Undoubtedly a preceding gonorrheal infection is not necessary to produce this variety of condolymata acuminata. Any discharge may cause irritation. If gonorrheal infection exists, it may be treated as has been described. Condylomata may be treated by cautery, caustics, or even strong desquamatives.

Other than these, the only tumors that have been described are angiomata of the urethra or the glans penis. Creite describes a penis cancer in a two year old child. However, this case is doubtful.

Englisch and Krebs describe polyps of the urethra resulting from a so-called hyperplastic form of polypoid urethritis. They also describe excrescenes and granulomata probably productive of uretheral inflammations. The author has seen polyp involving the entire urethra in young individuals. Polypi are found most frequently in the anterior urethra.

The symptomatology may vary with the obstruction. There may only be itching or tingling sensations, or frequency, or even inability to pass urine.

Circumcision.—Circumcision or posthectomy is the complete or partial removal of the prepuce or foreskin.

Indications.—The operation is carried out soon after the birth of a child either as a religious custom or as a hygienic measure. In older children the operation is indicated in any of the following conditions: Congenital phimosis if accompanied by hydrocele, hernia, balanitis,

preputial calculi, or by general or reflex symptoms clearly referable to the local condition. Hydrocele or hernia may result from straining at micturition; calculi may result from the retention of smegmal secretions. Some consider that an abnormally long prepuce, or a prepuce showing a fissured or eczematous condition call for its removal.

Unless there are urgent reasons operation should be deferred until the organ is large and easy to work with. Patients with hypospadial hoods should rarely be operated on in early life as such hoods may be of great value in connection with plastic operations undertaken later.

It should be remembered that at birth and during early infancy the prepuce is longer than the penis and its orifice narrow, so that a greater or lesser degree of congenital phimosis usually occurs. Besides this there may be a close adherence of the prepuce to the gland, which in some cases becomes more marked as time progresses. The phimotic condition generally has completely subsided by the age of puberty and of itself is not an indication for circumcision.

Operative Technique.—The operation should always be done under strict asepsis, and the use of an anesthetic either local or general is advised. Various methods have been devised. In general, the main idea is to avoid removing either too much or too little of the prepuce. It is usual to mark the outside of the skin when it is not under traction immediately over the bulge of the corona glandis. The skin mark should be traced all around the organ. The prepuce is then retracted, cutting the orifice if necessary. The prepuce is incised on the dorsum as far back as the corona and the flaps are trimmed away carefully to the extent as marked, after carefully freeing any adhesions found between the prepuce and the gland. The amputation may be done through the slot of a phimosis forceps. If this is used the inner layer of the prepuce is left. This inner layer is split dorsally and trimmed off on each side close to its attachment to the corona.

Some surgeons prefer a simpler and more rapid method, which is to make a transverse incision obliquely from behind forward and above downward in the direction of the corona glandis. After the prepuce has been sectioned the integument slides back on the penis, while the inner layer still covers the glans. This may be turned back if there is no constriction or divided as far as the corona by cutting or tearing along its dorsum. The flaps are trimmed away. The edges of the two layers are united by fine catgut sutures, but in very young children this is unnecessary and is usually omitted. In young children care should be taken to thoroughly disinfect the wound after the passing of urine and to change the dressings. Some surgeons prefer leaving the wound exposed without a dressing. In any case a light iodoform gauze dressing is sufficient.

I am inclined to believe that in connection with a large number of the cases that demand circumcision it is desirable at the same sitting to make a meatotomy. This naturally depends on the size of the external urethral orifice. Furthermore, particularly in those cases in which a meatotomy is advisable, I see no objection to

removing a portion of the frenulum, in other words, to do a frenulectomy. In these small children it only requires the the nurse takes care that the surfaces after a meatotomy do not become adherent. When frenulectomy is indicated and the frenulum is attached at the lower edge of the external urethral orifice, it should be cut with scissors to the posterior angle of the corona. From this to the inner leaf of the frenulum a varying amount of tissue, in V-shape, should be removed. The edges should be brought together with interrupted catgut sutures and as the frenular artery and vein are frequently in the portion of the frenular removed, care should be taken that these are securely tied. When this operation is omitted the true hygienic value of circumcision fails, as all venereologists will recognize that a short and tense frenulum is liable to traumatism and infection in later life.

Complications.—Too much or too little of the prepuce may be removed. In the former case inflammation and suppuration may occur with a contracted cicatrix. In the latter case phimosis may recur.

Severe and even fatal hemorrhage may occur from injury to the small vessels of the frenum, prepuce, or gland in tearing away adhesions, etc. Bleeding when severe must be stopped by ligating.

To avoid the very extensive disclosure of the glans caused by circumcision, modified operations have been suggested. Daget makes longitudinal incisions which are transversely connected. Longuet made what he terms a postheplastic posthetomy, slightly stripping the preputial ring with the scissors and incising the mucosa on the median line.

Edema of the Scrotum.—This condition is comparatively frequent and at times reaches extreme proportions because of the extreme laxity of the subcutaneous tissues of the parts. The edema may be part of a general anasarca or may be the result of local circulatory obstruction. Edema may likewise result from rupture of a hydrocele or from subcutaneous incisions. Inflammatory edema is not uncommon.

Symptoms.—Edema scroti may assume enormous proportions in cases of general anasarca and may extend over the entire penis. It may be of such proportion that the children must lie in bed with widely separated limbs. The skin is tense and glistening, and in the later stages the tension may give rise to pain or there may be added inflammatory symptoms. Edema due to circulatory disturbances is rare and rarely reaches the proportions of the edema due to general anasarca. Edema due to rupture of a hydrocele develops rapidly and its appearance corresponds to the side on which the hydrocele developed. *Inflammatory edemas* of the scrotum are common. The etiology of scrotal edema is varied and among the causes are all those productive of general anasarca. Tumors which compress the vena scrotalis cause local edema. Pressure from bandages, sutures, and other operative interferences may cause the condition. Inflammatory conditions in

the neighborhood of the scrotum, especially of the penis and perineum, are common causes. Gangrene may occur in the extreme cases.

Gangrene of Scrotum.—This is usually the result of deep-seated foci of inflammation spreading to the scrotum, but may originate from suppurating inguinal glands, or inflammation of the prepuce, or may be due to erysipelas of abdomen or thigh. Again, it may be due to traumatic rupture of the urethra.

Urethral Diverticula.—Urethral diverticula in children have been given very little study and have received little attention in the litera-

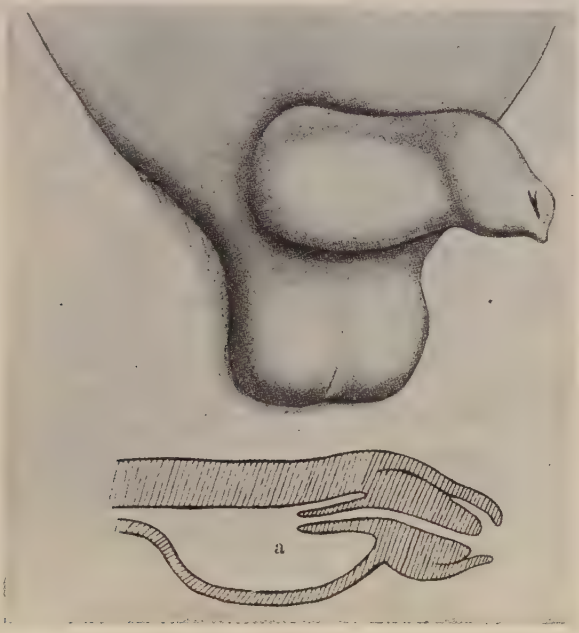

FIG. 202.—Diverticulum of urethra. *a*, Showing sagittal section. (Hueter.)

ture (with exception of studies and case reports in Gerhardt's Handbuch (Bokai) and a later article by Bokai (Jahrb. f. Kinderheilk.).

By urethral diverticula is meant a urine-containing sacculation, a bulging out of the urethra (ausbuchtung or poche urineare, of the French).

True or **false** diverticula must be differentiated, as to whether the inner wall is covered with mucosa or by newly formed cellular tissue. Depending upon their origin, they may be classified as follows:

(*A*) *True diverticulæ:*
1. Originating from congenital cause.
2. Not of congenital origin.
   (*a*) Caused by calculi.
   (*b*) By organized narrowing.

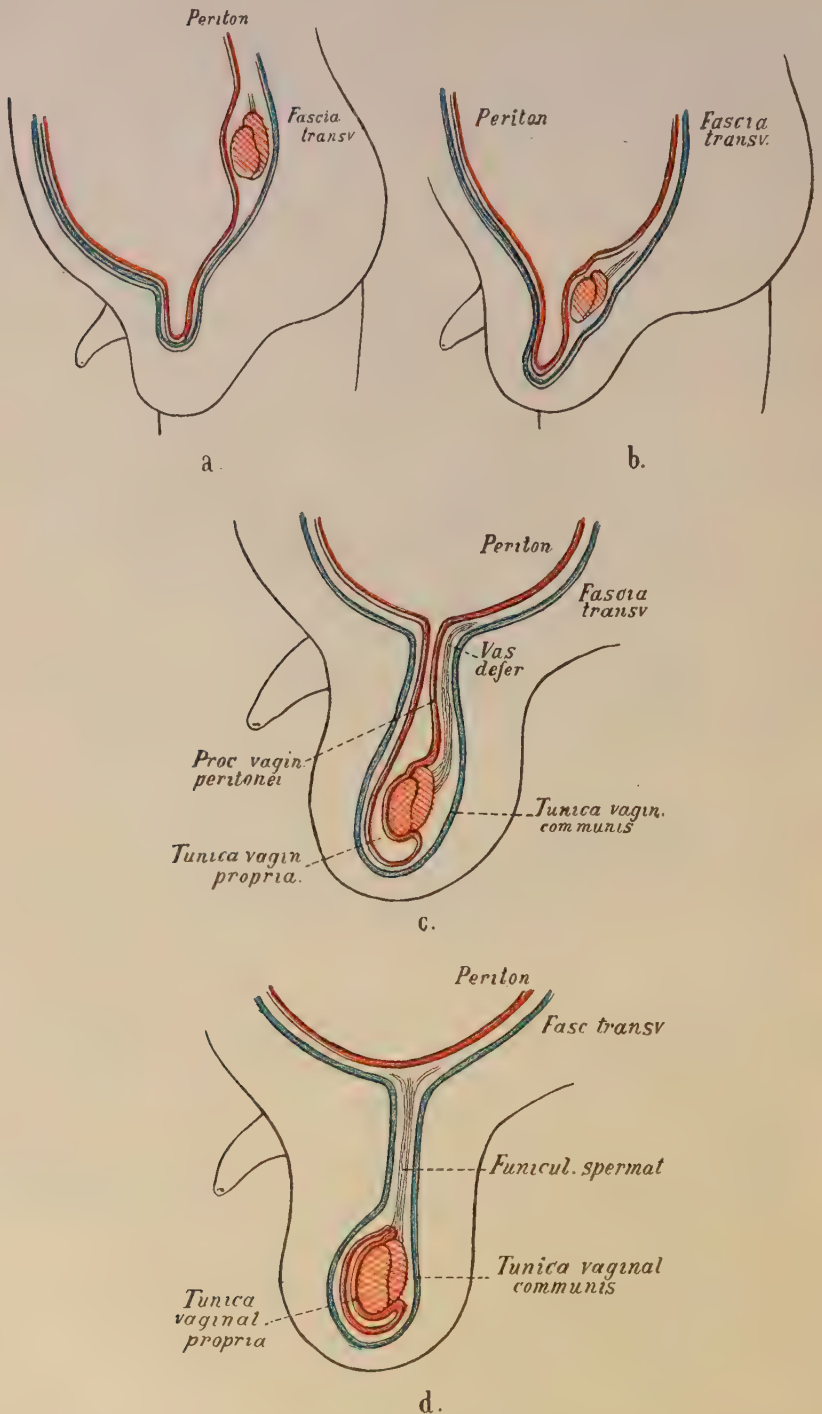

FIG. 203.—Showing origin of tunica from peritoneum. (Pfaundler and Schlossmann.)

(*B*) *False diverticulæ:*

1. Caused by stricture or internal injury of the urethra, for example, by urethral calculi, foreign bodies or instrumentation. An abscess may be formed in the neighborhood of the urethra, breaking into the urethra and forming a urethral pouch.
2. Independent of the urethra, for instance, from external trauma, an abscess develops in the neighborhood of the urethra, which leads to the formation of a urethral pouch.

True diverticulæ have been noticed in but a few instances and in practically all these cases the congenital origin has been convincingly proved. Bokai, Heuber, Pitz, Schleicher, Dutel, and others have reported cases.

The size of urethral diverticulæ varies from an almond to a hen's egg or fist.

Location.—They have been found between the fossa navicularis and the bulbous urethra and may extend this entire length. While in adults the diverticulæ are chiefly found in the perineal region, this location is exceptional in children. The almond to fist-sized diverticulæ did not in any of the reported cases extend beyond the penoscrotal furrow.

Etiologic factors other than those mentioned may be urethral valves, causing obstruction to outflow of urine, or there may be the congenital urethral pouching.

Urethral Fistula.—A urethral fistula is an abnormal opening in the urethra through which urine escapes during micturition. These fistulæ may be congenital during intra-uterine life. They may be classified as peni-fistulas, urethro-perineal (scrotal fistulas), and urethro-rectal fistulas.

Etiology.—They may be congenital. Outside of the congenital they may follow traumatism. Lodging of foreign bodies may cause perforation of the urethral rectal wall or any other point of the urethra leaving a fistula. Inflammatory conditions following traumatism and infection, malignancy, and tuberculosis are etiologic factors.

Abnormalities of the Penis.—Absence of the penis is rare. The penis may be completely absent while the scrotum and testicles are normally developed (case of Vinogrodoff, quoted by Guiteras), or neither penis nor scrotum are present, or the penis and anus may be absent.

Rudimentary Penis.—This abnormality of development is often seen and may occur with absence of testicles and scrotum.

Displaced urethra may be found, in cases of absent penis, with its orifice in the rectum or some fold in the skin, or with a more or less rudimentary penis. The urethra may be found coursing through the scrotal tissue independent of any corpus spongiosum, opening at any point between the penoscrotal junction and the glans, as in a case recently seen by the author.

Concealed penis is at times observed, especially in infants, the penis being embedded beneath the fat of the mons or hidden by the folds of a cleft scrotum. Careful examination will reveal the organ as a small, firm cylinder.

Treatment.—Operative interference to remedy this defect consists in incising the overlying tissues, liberating the organ and making use of the adjoining skin for flaps sufficient to cover it.

Multiple Penis.—This is of rare occurrence, although several instances are recorded in the literature. They may be separate or situated beside or over one another. The urinary function is usually not interfered with.

Imperfect or deformed penis is also associated with cases of true or pseudo-hermaphro latismus, many of which are quoted by different authors.

Absence or complete obliteration of the urethra is rare and usually is fatal by causing congenital hydronephrosis. If born alive, the child passes urine either through a perineal or rectal fistula or a patent urachus.

Congenital Tumors of the Prepuce.—Cysts are occasionally found, particularly in cases of elongated foreskin, anywhere on its inner or outer leaf. They are most commonly the size of a pea, though often are much larger. They are benign and of no particular importance unless of considerable size. They are removed in circumcision. However, they can be removed independently if the foreskin is not sufficiently long to demand circumcision.

Urethritis in Male Children.—Urethritis occurs in male children in three forms:

1. Simple urethritis.
2. Urethritis complicating other conditions.
3. Specific or gonorrheal urethritis.

1. Simple Urethritis.—Simple urethritis is common in male infants and young boys and is most frequently observed in children of the poor in crowded sections of large cities.

The causes are uncleanliness and irritation from soiled garments, foreign bodies, promiscuous handling and masturbation, and from phimosis and adherent prepuce. An inflamed prepuce and balanitis are frequent inducing factors. The inflammation is usually not extensive, involving seldom more than the orifice of the urethra and the fossa navicularis, although it may extend somewhat beyond those limits. The posterior urethra is never involved.

Few symptoms occur beyond the burning and irritation from the inflamed glans and prepuce. Occasionally difficulty in urination exists, accompanied by some pain. The discharge is often rather thin, watery and very foul, but may be copious and creamy or yellowish green. The microscope shows pus, epithelial cells and various bacteria, the commonest of which are cocci and diphtheroid bacilli. A study of the coccus forms shows that they may exist as diplococci, some of which

retain the Gram stain while others lose it. It not infrequently happens that intracellular Gram-negative diplococci, strongly suggestive of gonococci, are observed. Fischer (1917, p. 366) states that this type may be highly contagious and persist for months.

The diagnosis and differentiation from gonorrheal urethritis is made by cultural and complement fixation tests, and by the milder character and more rapid subsidence of inflammation in the simple form. Graham (1916, p. 570) and Still (1911, p. 566) mention the confusion that is apt to arise by reason of the various cocci and diplococci found in stained preparations of the exudate, and Still very properly cautions one against forming a hasty diagnosis, since diplococci other than gonococci are commonly present and are sources of error.

Treatment.—The treatment consists in removing the sources of irritation and maintaining antisepsis and cleanliness. Hot sitz or full baths are recommended. The bowels should be regulated and the fluid of the diet may be increased. Local bathing with warm physiologic salt solution, saturated boric acid solution, or 1:10,000 permanganate of potash should be frequent, and the diaper or other dressing changed every few hours. Urethral irrigation is contra-indicated. Under mild measures the inflammation usually subsides quickly, and when it terminates a circumcision is advisable.

2. Urethritis Complicating Other Conditions.—Under this heading are grouped the rare cases which seem to be associated with and directly caused by severe malnutrition and the cachectic state. These cases correspond to those of urethritis and vulvovaginitis in female children, which often endure for months in spite of treatment, and clear up only with improvement in the general health. There is usually a slight, but often irritating discharge, the microscope showing very few pus cells but quantities of epithelial cells and a preponderance of bacilli of the diphtheroid type.

Jacobi (1910, p. 770) mentions cases of urethritis complicating mumps, and cites Rilliet and Sanné who observed in a school epidemic 10 cases of orchitis of which five had urethritis with a yellowish, tenacious discharge.

3. Specific or Gonorrheal Urethritis.—While gonorrheal urethritis is far less frequent in male than in female children, in which it is associated with vulvovaginitis, it nevertheless is the commonest form of urethritis. It occurs at all ages of childhood from infancy to puberty, but by far the greater number of cases are observed after the sixth year. Holt (1916, p. 634) cites a report of Poynter on a case in a boy of three years infected through his nurse. Kerley mentions a case in a boy of four in which the infection was acquired from an older sister. Cautley (1910, p. 594) mentions a case reported by Apert and Froget in an infant boy of 10 months. The literature and private case histories lead to the belief that gonorrheal urethritis is by no means uncommon in boys between the ages of 10 and 14.

The disease is invariably acquired by contact with an infectious source, and is due to the activity of the "micrococcus gonorrhœa,"

sometimes called the diplococcus, or gonococcus, of Neisser. The indiscriminate statement that contact with bed clothes, towels and linen is responsible for many cases of infection rests upon very unsatisfactory data. Indeed this is the usual excuse where the source is difficult to trace. It is true that in the moist state the gonococcus may remain viable for considerable periods of time, but it is practically impossible to recover the organism from secretions spread upon cloths after a two hour interval of exposure to the air. Warden* has shown that the germ remains viable for days in glycerin, ointments and toilet creams, and may be recovered in culture from the fingers and hands after several hours, particularly if they remain moist or covered with emollients. The usual infectious sources are the hands and genitals of nurses, relatives, or older playmates.

Diagnosis.—The diagnosis is made by demonstrating the presence of the gonococcus either by culture, or by the serum test for antibody by the method of complement fixation. Diagnosis by the microscopic examination of stained smears is always open to question in subacute and chronic cases, and often in acute cases. It is permissible only when no other organisms are present, and when, in early cases, the cocci have a characteristic morphology and intracellular arrangement. The Gram stain is unnecessary and may be misleading, since staphylococci and other cocci may, under certain conditions, lose the Gram stain. Warden* has made artificial preparations with leukocytes and staphylococci in the presence of serum indistinguishable from the microscopic picture seen in gonorrheal smears, and has demonstrated further that the diplococcus or "biscuit" form is not peculiar to the gonococcus but is common to many varieties of the coccus family, especially during growth in the body fluids, and that in this form they are not uncommonly Gram-negative. It should be borne in mind also that the diphtheroid bacillus, commonly found in the urethra, often appears in diplococcal forms.†

The best culture medium for routine diagnosis of gonorrhea is nutrient beef or veal broth-agar, neutral to phenolsulphonephthalein, to which has been added before slanting or pouring 2 to 5 per cent. of sterile defibrinated rabbit blood. This medium should be dry rather than moist for the reason that excess of moisture favors early autolysis of the cocci and "blasting" of the young colonies. The differential diagnosis between gonococcus and other cocci is an easy matter to the bacteriologist trained in the examination of colonies on culture media.

The diagnosis by complement fixation requires a few words of explanation. A positive test is of value, whereas a single negative test is of no value whatever. It has been observed by several writers, among others Irons,‡ Warden§ that gonococcus antibody may be present

* J. Infect. Dis.

† Fox, Studies in diphtheroids III. Arch. Int. Med. (Sept. 15, 1915).

‡ J. Infect. Dis. (March, 1915).

§ J. A. M. A., lxv (1915), p. 2080.

in the blood of the patient only at intervals during an attack of gonorrhea, indicating that it is in all probability produced periodically and in small amounts, so that the graph or curve appears wave-like. It is possible then to obtain a negative serum test when gonococci are still recoverable by culture. On the other hand, repeated negative tests in the absence of demonstrable gonococci are of distinct value. Much depends on the antigen employed. Warden and Schmidt* observed the superiority of an alcoholic solution of specific gonococcus fats, as antigen, over aqueous suspensions and autolysates of gonococci. They reported the results of several hundred tests, since which time the fatty antigen has been employed in over 8000 tests. The original conclusions have been strengthened, that is, that a larger number of positive tests are obtained and that the fluctuations in the tests are less marked. In one series of 1000 tests it was observed that positive diagnoses were made in 70 per cent. of the cases whereas the examination of smears led to positive diagnoses in only 35.6 per cent. of the same cases.

Symptoms.—The symptoms are as a rule more severe than in vulvovaginitis but less so than in adult males, although the local inflammation may be considerable. In uncircumcised boys the prepuce is commonly edematous, and inguinal adenopathy frequently occurs. Pain on urination and painful erections are not unusual. Constitutional symptoms are less common in children than in adults. Balanitis is often coincident. The course of the disease is apt to be protracted and extend over a period of weeks, often months.

The commonest complications are posterior urethritis and cystitis. Epididymitis may occur, but orchitis is very rare. Arthritis frequently appears as a phase rather than a complication. Still and Goodheart (1911, p. 566) cite Lucas' report of a case showing arthritis at birth along with ophthalmia. Willard (1910, p. 582) gives a report by Holt on 26 cases of arthritis, in an epidemic, of which 19 were boys, and in which of seven girls only two showed vaginitis. Jennings† on the other hand, states that the invasion of joints and heart is almost unknown. Our own experience leads to the belief that the older the boy the greater the liability of joint involvement. The larger joints are those most frequently affected.

Unquestionably gonococcus sepsis and endocarditis are exceedingly rare in young children. Fischer (*ibid.*) cites the report of Leyden of Berlin of gonococcus endocarditis in infancy.

In spite of frequent reference to conjunctivitis in the literature it is not a common complication. Indeed it is surprising that conjunctivitis is so infrequent in gonorrhea in both boys and girls, and one is led to infer the possibility that the local genital infection may confer some degree of immunity on the membranes of the eye—at least against the same strain of gonococcus.‡ Fischer (*ibid.*) mentions pyelitis as a rare

* J. Lab. and Clin. Med., i (1916), p. 5.
† Carr (1910), p. 761.
‡ In this connection *vide* L. Pearce, J. Exper. Med., i (April, 1915).

complication. Stricture of the urethra should be looked for in every case, although it does not appear to be relatively so frequent as in adult males.

Treatment.—The treatment consists of keeping the patient in bed until the acute manifestations have subsided. Frequent warm sitz or full baths are desirable. The diet should consist largely of fluids, and the bowels must be kept freely open by enemata or mild salines, or castor oil. Alkaline waters may be given by mouth. Sandalwood oil in milk, or in capsules, should be administered. Sedatives against pain and irritation are best given in the form of rectal suppositories.

Local treatment consists in maintaining rigid cleanliness and antisepsis, even though the patient be properly isolated from other children. There should be frequent flushing of the parts with warm saline solution, 1 : 5000 permanganate of potash solution, or 1 : 10,000 bichlorid solution. In case of phimosis the orifice must be stretched and adhesions severed so as to insure that the solutions reach all areas. Following the external irrigations, the parts may be bathed with from 2 to 5 per cent. argyrol, and covered with voluminous gauze dressings moistened with a mild antiseptic. During the acute stage, and so far as is possible throughout the disease, urethral injections and instrumentation are to be avoided. In boys of 12 to 14 instillations of argyrol or its equivalent may be cautiously given after all acute signs have passed. The indications for the use of sounds, following the cessation of all discharge, should receive careful consideration by the practitioner. Complications should be managed in the same manner, so far as is possible, as in adults.

The constitutional treatment by means of vaccines, stock or autogenous, or by antigonococcic serum, is not be to commended. The most rational plan of systemic treatment is that worked out by Warden,* which consists of intravenous inoculations of the specific gonococcus fats in aqueous solution. This plan is based on experimental facts. He has shown† in immune reactions resulting in the lysis or destruction of cells, bacterial or somatic—such for instance as the solution of cholera bacilli in the Pfeiffer phenomenon, the hemolysis of red blood-cells, etc.—that complement of the blood is bound by the specific fat antibody combination equally well as by the antigen (cell) antibody combination (as shown by complement fixation tests). In other words, the fats specific to each cell are able to replace the cell itself in the immune reaction.

The aim of the treatment, therefore, is twofold—to increase the quantity of specific antibody and to facilitate the operation of immune reaction within the body of the patient. The inoculations accomplish this by imitating the body's own process in the course of an infection. When germs invade the body in sufficient numbers the physicochemical state of the blood and cells is altered by them in such a manner as to produce a systemic response manifested by more or less intense rigor,

* J. A. M. A., lxviii (1917), p. 432.
† J. Infect. Dis.

fever and malaise, that is, the ordinary symptoms of oncoming infection. This response also mobilizes what may be called general or non-specific antibody. The germs, or other cells, have, however, a further effect, namely, the mobilization of specific antibody through the influence partly of specific substances within themselves, and partly by the physicochemical effect of these specific substances on the fluids and cells of the body. These effects are produced by the intravenous injections in the following manner: The first effect is produced by the watery portion of the injection, by simple dilution of the plasma and consequent aggregation of its euglobulins, the second by the specific gonococcal substances contained in the fatty portion. The complete rationale of the treatment is too complex for extended exposition in a brief chapter. Suffice it to say that it has proved its efficacy especially in acute gonorrhea in adults. Those interested should consult the original papers.

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CHAPTER CVII

DISEASES OF THE FEMALE GENITAL ORGANS IN CHILDHOOD

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Introduction.—A discussion of the diseases which affect the female genital tract in childhood need not occupy any considerable space in a treatise on diseases of children. From the time of birth to puberty the genital organs may be said to be in a latent or quiescent stage. It follows then that inasmuch as these organs do not functionate until menstruation and the capacity for childbearing is established, they do not, at this period of life, develop any of the disorders incident to maturity, childbearing, or rarely to sexual intercourse.

It is true that gonorrheal infections in the newborn and in later childhood, which are to be fully considered elsewhere in this treatise, constitute an important chapter for the consideration of the pediatrician. Yet in a larger sense, gonorrheal infection of the genital organs in infancy and childhood seldom approaches in its pathologic and clinical aspects the complexity which it presents in mature life, for the reason that the disease seldom passes beyond the limits of the vulva and vagina. In the experience of the author, there has been but one exception to this statement; that of a girl of three years of age, infected by her mother, who had in turn acquired the infection from the father. In this case the infection spread rapidly from the vulva to the vagina, thence through the uterus and tubes to the pelvic peritoneum, and resulted in the accumulation of approximately two liters of gonorrheal pus in the pelvic and abdominal cavities. As with gonorrhea, so with all manner of infections which involve the female genitalia in childhood, the resultant inflammation is almost invariably confined to the lower genital tract. Furthermore, such infections rarely persist over a great period of time and, therefore, do not, as a rule, leave their imprint upon the genital organs in mature life.

Displacements of the uterus and its appendages, with the exception of prolapsus, which is far from common, deserve no consideration, inasmuch as they have no clinical bearing until puberty is established.

Tumor formations of the genital organs in childhood, though rarely observed, are when encountered, of the most serious consideration, inasmuch as a considerable proportion of these tumors are malignant and if not recognized promptly will of necessity end fatally.

Likewise, injuries of the genital organs seldom occur in the absence of childbearing and operative intervention and, therefore, demand scant consideration in a work of this scope.

On the other hand, malformations and maldevelopments of the genital organs are pertinent topics for the consideration of pediatricians, in that anomalous developments not only exist in the period of adolescence, but should be recognized at this time because of their effect on the later years of life.

Finally it should be emphasized that the functional disorders of puberty should receive careful consideration, since they may be forestalled in part by the proper management of the child in the period of adolescence. To foresee such possible disorders and to safeguard the child in its early development by the exercise of hygienic management is the part of wisdom.

Malformations of the Female Genital Organs.—Introduction. Malformations of the sexual organs of the female child have little or no bearing upon the physical welfare of the individual but are of the utmost significance in relation to future menstrual phenomena and to the sexual and reproductive functions of the matured woman.

These malformations of the genital organs differ from anomalies in development in other portions of the body, in that they develop in part after the birth of the child. This phenomenon is explained by the fact that the uterus and its appendages do not attain full development until the time of puberty. It follows that post-natal anomalous developments are found in the female genital organs. Furthermore, it is to be borne in mind that under perfectly normal conditions there is a physiologically latent period which extends to puberty, so that prior to this period no physiologic disturbance can be expected to arise as the result of any existing anomaly in development. It follows then that because of the absence of function on the part of the genital organs of the female up to the time of puberty, such anomalies as may exist are not usually recognized before that period.

Ballantyne says: "Teratology and embryology depend upon each other; the one helps to explain the other; the one without the other would be an indecipherable legend. Malformations are simply disorderly formations and teratology is nothing more than the pathology of embryology."

It is not safe to venture a definite statement on the causes of malformations of the genital organs. It is fair, however, to assume that they are the same as the causes which bring about anomalies in the development of organs located elsewhere in the body. Heredity and nutritional changes are doubtless important factors and suggest the possible rôle played by syphilis, alcoholism, and toxemia in the prenatal state.

The key to a correct understanding of the various anomalies of growth of the genital organs is their embryologic development, since faulty development is but a check upon the normal process of development in the embryo. We are to bear in mind that the sexual organs of

the female are derived from three distinct and separate embryologic structures: The Wolffian body which gives origin first to the sexual gland and then to the ovary; the Müllerian ducts from which are derived the Fallopian tubes, uterus, and vagina; and finally the cloaca from which the various structures of the vulva are formed. From a knowledge of these facts, it can readily be seen that anomalies in the development of one of these structures does not necessarily imply faulty development in genital organs which are of separate origin. To illustrate, we may find a case of an atresic vagina, where, nevertheless, the internal genitalia are fully developed. Again, on the other hand, we may find the vulvar structures fully developed and the internal genitals under-developed or malformed.

FIG. 204.—Diagram illustrating development of lower urogenital tract. The ureters and Wolffian ducts open at the same level in the urogenital canal: *a*, Urogenital canal; *b*, rectum; *c*, Wolffian ducts; *d*, ureter. (After Nagel.)

Development of the Female Genital Organs.—The Ovaries.—The embryo is sexually indifferent in its earliest state of development. The first suggestion of sex is found in the germinal epithelium situated on either side of the lumbar vertebræ.

FIG. 205.—Diagram illustrating development of lower urogenital tract. The vagina (*a*) is represented well developed. Above it is a remnant of the Wolffian ducts (*b*): *c*, Rectum; *d*, bladder. (After Nagel.)

FIG. 206.—Diagram illustrating development of lower urogenital tract. The Wolffian ducts and ureters are represented as opening into the urogenital canal at different levels: *a*, Bladder; *b*, rectum; *c*, urogenital canal; *d*, ureter; *e*, Wolffian duct; *f*, Müllerian duct. (After Nagel.)

From this germinal epithelium the genital or sex glands are derived which later give form to the ovaries in the female and to the

FIG. 207.—Section of normal infant's pelvis. (Graves "Gynecology.")

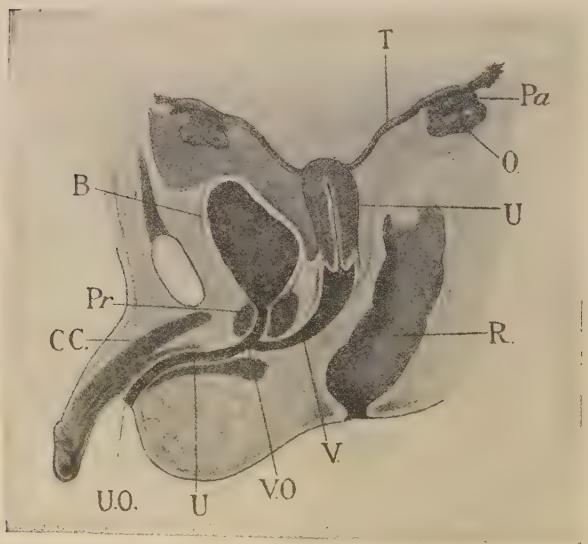

FIG. 208.—Diagrammatic sagittal mesial section of atypical female sex-ensemble (female pseudo-hermaphrodite). Note the vagina ending in the prostatic sinus, the prostate and the simulated hypospadias. *T*, Fallopian tube; *Pa*, parovarian; *Pr*, prostate; *U*, uterus; *R*, rectum; *V*, vagina; *U*, urethra; *B*, bladder; *UO*, urethral orifice; *VO*, vaginal orifice; *O*, ovary; *CC*, corpus cavernosum. (Tibiger.)

testicles in the male. The genital glands make their appearance at about the sixth week, but it is not until about the end of the twelfth week that the female organ is clearly differentiated from the male, and not until puberty is well established may they be considered fully developed.

At about the third month of fetal development, the ovary begins its descent from the lumbar region to the pelvis. This descent is

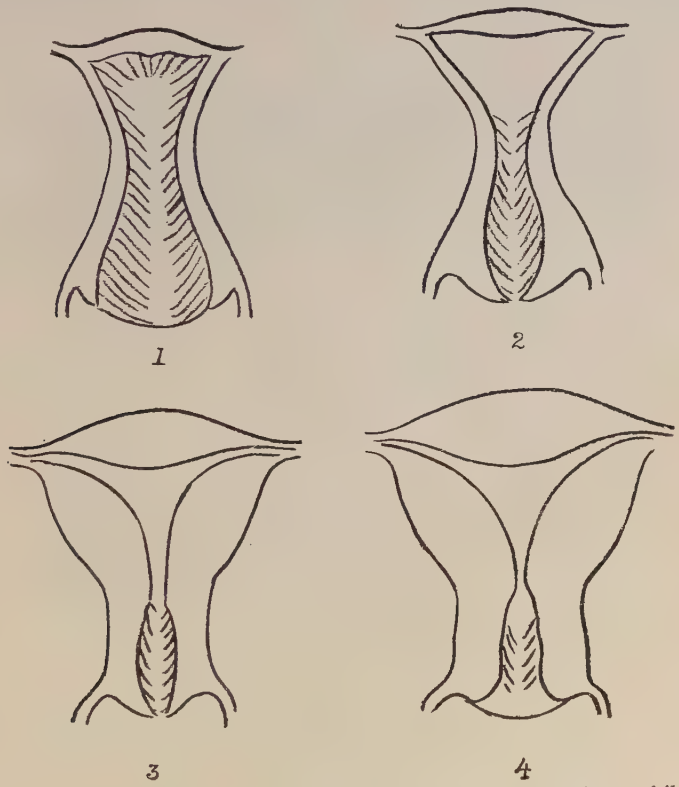

FIG. 209.—Development of the uterus. 1. Uterus of newborn child. The cervix shows much greater development than the body. The folds of the arbor vitæ reach from the cervix to the top of the uterine canal. 2. Uterus of a seven-year-old child. The body is equal in development to that of the cervix. The folds of the arbor vitæ reach just beyond the internal os. 3. Uterus of a mature virgin. The development of the body excels that of the cervix. The folds of the arbor vitæ reach only to the internal os. 4. Uterus of a woman who has borne children. The body shows a still greater development. The folds of the arbor vitæ occupy only about two-thirds of the cervical canal. The external os of the cervix is dilated. (After Küstner.)

accomplished by the gubernaculum of Hunter which is first recognized as an abdominal fold and is later reinforced by muscle fiber and connective tissue. This structure passes from the Wolffian body to the inguinal canal in its early development and is responsible for drawing the ovary into the pelvis. It is from this structure also that the round

and suspensary ligaments of the ovary are derived. The complete descent of the ovary is not accomplished prior to maturity. Throughout infancy and childhood it remains high in the pelvis.

We can now understand how the ovaries, like the testicles, may fail to descend, and how supernumerary bits of the organ may be found in the path of its descent.

The Fallopian Tubes, Uterus and Vagina.—In the early embryo, we find two solid cords passing from a point external to the Wolffian body downward and inward to the urogenital sinus. These cords are

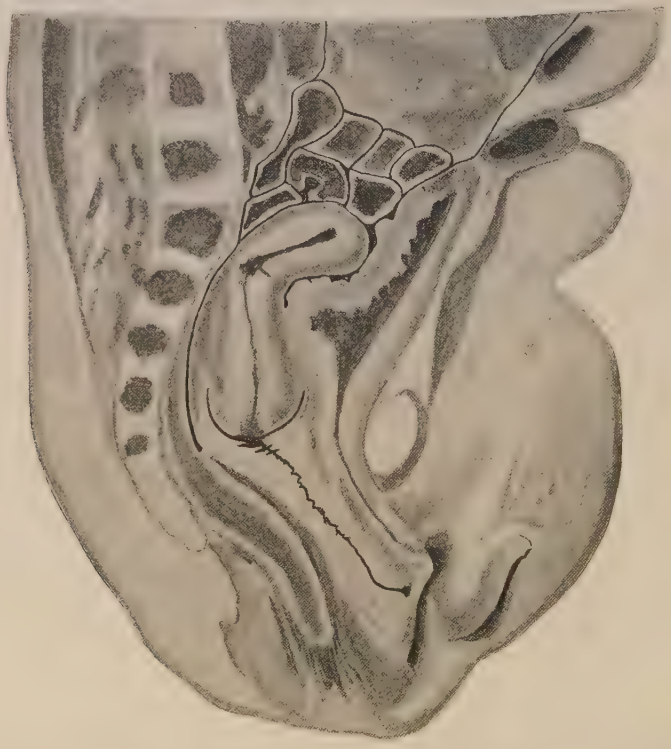

Fig. 210.—Vertical mesial section of fetal pelvis of large fetus at time of birth. (Webster, "Diseases of Women.")

later channeled out and lined with columnar epithelium to form the Müllerian ducts. By development and fusion, these ducts form the Fallopian tubes, uterus, and vagina. Fusion begins at about the ninth week and proceeds from below upward; first to form the vagina, next the cervix, and finally the body of the uterus. Beyond this point there is no fusion, the Fallopian tubes remaining separate and divergent. Anomalies in the development of the vagina, uterus, and tubes arise from failure of the ducts to become channeled out or to fuse properly. Hence, we occasionally encounter atresias and the doubling of the vagina, cervix, and body of the uterus. By the ninth week the ducts have fused at their lower extremity to form the vagina, but

do not channel out to make this organ hollow until some weeks following the channeling of the uterine portion of the ducts. It is not until the fourth or fifth month that the uterus and vagina communicate. In fact, complete fusion of the uterus is not accomplished prior to this time. The cervix comes into evidence also at about this time, as does the hymen at the lower segment of the vagina.

The Vulva.—The development of the external genitals is more complex than that of the internal organs. The ectoderm invaginates

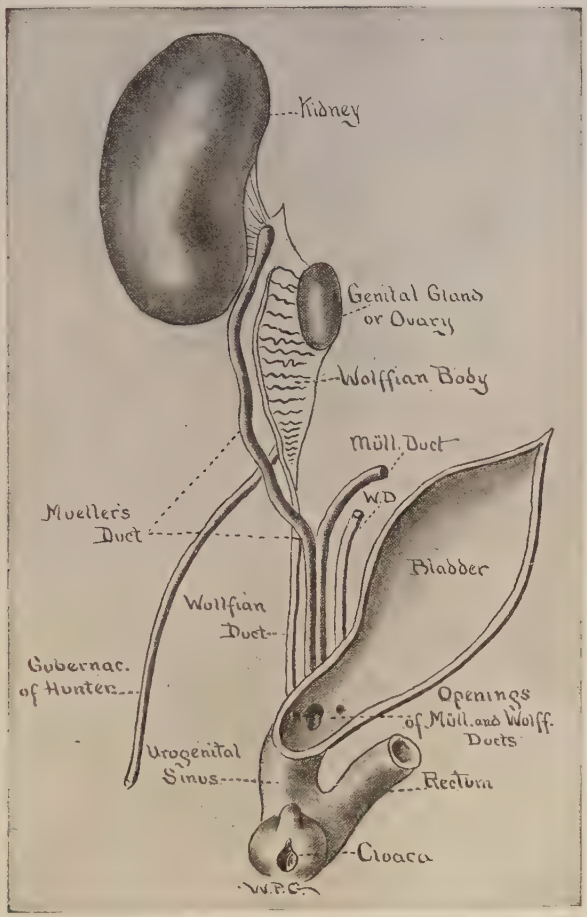

FIG. 211.—Diagram showing the relationship of the Müllerian and Wolffian ducts and their openings into the urogenital sinus. (Graves "Gynecology.")

at the lower pole of the embryo and communicates with the cloaca to form the primitive anus. The anterior part of the genital plate thickens to form a prominence known as the genital tubercle, which is the anlage of the clitoris and nymphæ of the female and the penis of the male. Later, a groove forms on the under surface of the tubercle and passes

backward into the cloaca. This is known as the genital groove. Folds on either side of this develop into the labia minora and labia majora. Next, a partition appears in the cloaca, and from this structure is developed the perineal body. In this manner the urogenital sinus is developed anteriorly into which open the urinary and sexual ducts. From such a complex development, we readily understand how some of the most perplexing anomalies may arise.

Malformations of the Ovaries.—Anomalies in the structural development of the ovaries are not common, and in infancy and early

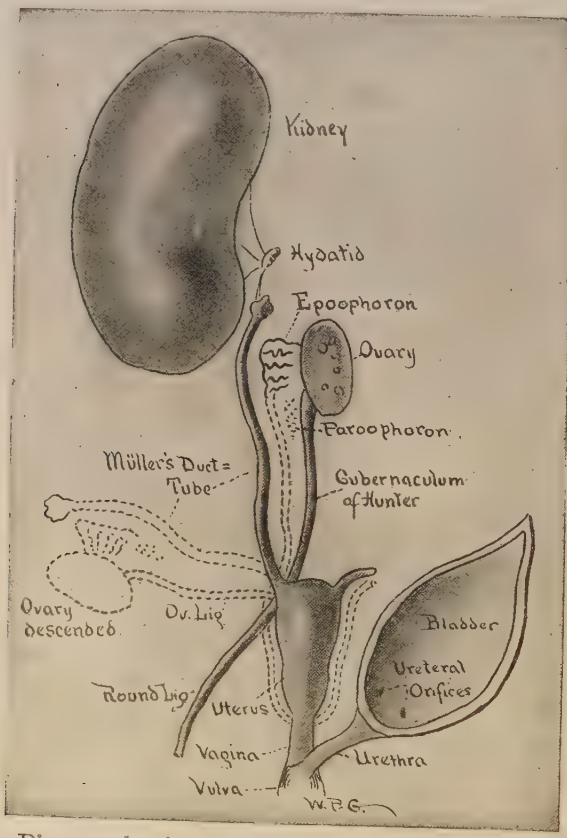

FIG. 212.—Diagram showing descent of ovaries and fusion of Müller's ducts into uterus and vagina. The way in which the gubernaculum of Hunter becomes the round and ovarian ligaments is shown. (Graves "Gynecology.")

childhood have little or no clinical significance. One or both ovaries may be absent or under-developed. A supernumerary ovary may be found, but more often such supernumerary structures are but isolated fragments of the parent ovary. The ovary may be found in localities remote from the usual seat; and finally, the ovary may be congenitally enlarged and endowed with hyperfunctionating powers.

Absence of the Ovary.—Entire absence of both ovaries, except in acephalic and sympodial fetuses, is a rare finding and is an almost invariable concomitant of the under-developed genitalia. In these cases it is reasonable to assume that a careful post-mortem dissection would probably reveal remote fragments of ovarian tissue. When one ovary is wanting and the other intact, the tube and half of the uterus corresponding to the defective side are likely to be under-developed or missing. The same may be said of the corresponding kidney.

Just what rôle the ovary plays prior to puberty is not known, and for this reason we have no knowledge of possible systemic and pelvic changes which may result from a lack of ovarian tissue in the years preceding this period.

After puberty is established, however, we know that the absence of a single ovary creates no disturbance in the menstrual functions and does not diminish the power of reproduction. A case in point is that of Lawson Tait, where, in spite of the fact that a tube and ovary were wanting, the woman gave birth to ten children. Where both ovaries are wanting or hypoplastic, the defect is certain to be manifest at puberty by the delay or absence of the menstrual flux, by sterility, and by the absence of changes peculiar to the pubescent period. The menses fail to appear, the body does not round out as is usual at this time of life, hair fails or appears late on the mons veneris; and it may be that the individual presents the infantile type with possible idiocy and cretinism. The mental development may be retarded. Epilepsy is known to develop about the time of puberty, while chlorosis is a common accompaniment.

Arrested development of various parts of the body is known as *infantilism*, the cause of which has often been attributed to hypoplasia of the ovaries. Proof of this, however, is wanting. The presence of hypoplastic ovaries associated with infantilism may be but an expression of a cause, as yet unrecognized, not only of infantilism in general, but of faulty development of the genitalia as well. That infantilism is not necessarily the result of ovarian deficiency is evidenced by a series of recorded cases where, in spite of the fact that the ovaries were hypoplastic and even in some instances wholly wanting, the general development, nevertheless, was not altered.

Rudimentary Ovaries.—Hypoplasia of the ovaries, in which the infantile type of the organ is preserved, is not a rare finding when we include all gradations of development. The follicular elements may be wholly wanting or at best may not go beyond the primordial stage of development. This implies that the ovarian secretions are deficient, in consequence of which the genital organs suffer in their development. All that has been said of the general and local results of absent ovaries will apply in a variable degree to rudimentary ovaries. As a result of such a condition, the uterus is under-developed; menstruation is delayed, scanty, or wanting; sterility is inevitable; the individual is neurotic, and is often the subject of chlorosis. Such ovaries are

believed to result from fetal oöphoritis and from torsion of the pedicle of the ovary.

Displacements of the Ovaries.—Congenital displacements of the ovary are rarely observed. The organ has been found attached to the lower pole of the kidney, to the cecum, in the inguinal canal, and even to the brim of the pelvis.

Supernumerary and Accessory Ovaries.—The only authentic case in which there was a third well-formed ovary attached to the uterus by a ligamentous band is that reported by von Wenkel. Seitz found five cases in the literature which presented a third ovary together with an excessory Fallopian tube. On the other hand, accessory bits of ovarian tissue more or less remote from the parent ovary are not rare findings. One observer found accessory bits of ovarian tissue in 5 per cent. of his dissections. Abberent ovarian bits have been found attached to the colon, cecum, intestine, omentum, and parietal peritoneum. It is of interest to record that abberent ovaries have given rise to tumor growths. They have also accounted for the persistence of menstruation after the removal of both ovaries and of pregnancy following upon double ovariectomy. The explanation for their presence most often presented is that fetal bands bite off bits of tissue from the parent ovary.

Malformations of the Fallopian Tubes.—One or both tubes may be absent or may retain the fetal type, which is that of a very much convoluted tube with a narrow lumen. In rare instances, in the absence of a lumen the tube presents a solid cord. Again there may be accessory tubes or ostia. Anomalies in the development of the tubes are commonly associated with malformed uteri and ovaries. Aside from being anatomical curiosities, they serve as an index to other possible deformities in the genital tract. In the period of sexual maturity they become a factor in the causation of sterility and tubal pregnancy, but throughout infancy and childhood they are of no clinical significance.

Malformations of the Uterus.—The malformations of the uterus are the most prevalent and interesting of all genital anomalies. Their pathogenesis and their influence on the general and sexual health of the individual is well known. Inasmuch, however, as the uterus does not functionate before the advent of puberty, they are only of interest to the pediatrician from a prognostic point of view.

In classifying the anomalous developments of the uterus we will here follow the suggestion of von Wenkel, who has formulated these anomalies into two main groups: The antenatal and post-natal malformations. Von Wenkel's classification is based on the theory of arrested development. A condition present in one stage is regarded as normal, but when persisting into a later stage it becomes abnormal, in that the development has been arrested. The following table will serve to illustrate the grouping of von Wenkel, slightly modified from that appearing in Reed's "Textbook of Gynecology."

GROUPS

Prenatal

1. (*a*) Absence of uterus, complete, together with absence of tubes and vagina (very rare).
   (*b*) One-horned uterus, with no trace of the other horn (uterus unicornis sine ullo rudimento cornu alterius).
2. (*a*) Externally double uterus (uterus duplex sine didelphys; uterus bicornis).
   (*b*) Solid or partly excavated uterus (uterus solidus, uterus rudimentarius, uterus partim excavatus).
   (*c*) Combination of (*a*) and (*b*) (uterus duplex solidus, uterus bicornis rudimentarius).
   (*d*) One-horned uterus, with other horn solid or partly excavated (uterus unicornis cum rudimento cornu alterius).
3. Uterus divided internally more or less completely, without or with external signs of duplicity (uterus septus, subseptus, uterus bicornis septus).
4. Uterus with flat fundus, with or without complete or partial internal duplicity (uterus planifundalis septus, subseptus, simplex).
5. Uterus with fetal characters (small body, large cervix).

Post-natal

6. Uterus with infantile characters (uterus infantilis).

Uterus Deficiens and Uterus Rudimentarius.—It is highly probable that in no case has the uterus been found wholly absent in an otherwise well-developed individual. Blair Bell cites a case in which there was complete absence of uterus, tubes and ovaries; the individual possessed female characteristics. On section, however, two testes were found in the abdomen. Ballantyne, commenting on this case, suggests that the ovaries and testes are not all powerful in determining the sex characteristics. Heredity, as an etiologic factor, is suggested by N. Noston, who found absence of the uterus in a family of three sisters and two cousins. In every instance where a careful ante-mortem or post-mortem dissection has been made, the uterus has at least been represented by a ridge of fibromuscular structure. In the acardiac twin, or in sympodial fetuses, complete absence of the uterus is of common occurrence. In some of the cases recorded as having no uterus, it has been suggested that the individual was a male with undescended testicles. Where a rudimentary uterus exists, the remaining genital organs are usually rudimentary also, though cases are on record in which the ovaries and vagina are fully formed. In such cases, the uterus fails to menstruate though menstrual molimina and vicarious menstruation may be experienced. Such an individual may take on the secondary characteristics of her sex, but she remains hopelessly sterile. No clinical distinction can be made between absence and a rudimentary state of the uterus. The most that can be demonstrated by a physical examination is that there is no fully formed uterus between the rectum and bladder

Weisswange records a case in which a rudimentary uterus in a girl 19 years of age was associated with vicarious menstruation (epistaxis).

Uterus Fetalis.—When the uterus, either late in fetal life or early in the post-natal stage, reaches a certain point in its development and proceeds no further, we speak of it as a *fetal uterus*. Instances of such occurrences are by no means rare and account for a certain, though small, percentage of cases in which amenorrhea, dysmenorrhea, and sterility are observed. Associated with a fetal uterus and the resultant functional disorders incident to its under-development there are often observed certain local and general manifestations of infantilism.

The cervix is no longer thicker than the body, and the whole uterus is small, giving the appearance of an inverted ninepin.

There is usually no cause for suspecting the presence of a fetal uterus before the advent of puberty, unless, perchance, the external genitalia are also malformed. When the uterus fails to develop beyond the fetal type, there can be no menstruation and no childbearing. If, however, the ovaries are well formed, though this is rarely the case,

FIG. 213.—One-horned uterus. (Ashton, "Practice of Gynecology.")

the individual may experience menstrual molimina. In rare instances vicarious menstruation is observed. Chlorosis is frequently associated with a fetal uterus, and there may be disorders of the cardio-vascular system. Treatment will be of no avail.

Uterus Pubescens.—The development of the uterus may proceed to a point somewhat short of that normally attained at puberty, in which the cervix and body of the uterus are about equal in size, as contrasted with the fetal uterus, in which the cervix is longer and broader than the body. The condition will not be recognized until sometime after the usual period of puberty. In such cases sterility is all but inevitable. It is doubtful if any effective treatment can be adopted. Corpus luteum, tonics, the galvanic current, and the stem pessary have all been tried but with negative or at best doubtful results.

Uterus Unicornis.—This is a condition in which only a single horn of the uterus may be developed, the other being rudimentary or wholly absent. The explanation lies in a complete or partial defect of one Müllerian duct. The single horn tapers into the Fallopian tube at the

uterine insertion of the round ligament; the vagina is narrow or septate; the cervix is small and conical. The ovaries may both be well developed; they may be rudimentary; or the one on the side corresponding to the developed uterine horn may be fully formed and the other undersized or absent. The kidney may be wanting on the defective side, and the urinary bladder may be deformed.

The condition may escape notice throughout childhood and adult life. The individual may menstruate and bear children, though it is exceptional for such a uterus to functionate normally.

Uterus Bicornis.—The Müllerian ducts may blend at their lower extremity to form the vagina, cervix, and the lower portion of the body of the uterus, leaving the segments which form the upper part of the body separate and diverging. Such a uterus is known as a bicornate. It is the connecting link between the double uterus and the septate uterus and is found in all grades of development, from a mere depression in the fundus to a complete separation of the two halves of the uterus down to the cervix. The vagina may be normal, infantile, septate, or subseptate. One or both horns may be imperforate. The condition may not be recognized in childhood or in adult life. Menstruation and childbearing may proceed normally, but ordinarily fertility is reduced. A bicornate uterus may be associated with abnormalities of other organs of the body such as ectopia vesicæ, floating kidney, cyclopia, and anencephaly.

Uterus Didelphys.—A double uterus is the result of failure of the two fully developed Müllerian ducts to unite. The two halves may may be well formed or one or both may be under-developed. The walls may be thin, and the cavity of either half partially or wholly obliterated. The angle of divergence of the two halves varies greatly. Along with the doubling of the uterus may be a double cervix and double vagina. What has been said of the uterus bicornate relative to its clinical aspects will apply also to the double uterus. Blair Bell records a case in which either half of the uterus lay in an inguinal sac.

Uterus Septus.—Externally the uterus may appear perfectly formed, but within is a septum which divides the cavity more or less completely into two lateral halves. This septum may extend from the fundus to the internal os and even to the vaginal outlet, or it may be found at any point from the fundus to the cervix. Where the septum is complete the term uterus septate is applied, and where it is but partially formed, the condition is known as *uterus subseptate.* Such a uterus may functionate perfectly and be of clinical interest only in relation to the presentation, position, and delivery of the fetus. The septum is discovered accidentally in the conduct of labor.

Uterus Accessorius and Trifid Uterus.—We do not here refer to a double uterus (uterus didelphys), the condition in which the two halves of a single uterus fail to unite. In the thoracopagous or pygopagous twins, each may possess a uterus, and each uterus may be provided with tubes and ovaries. Each of the twins, on the other hand, may

have a double uterus from failure of the ducts to fuse. Where the twins have two heads, two bodies, a single pelvis, and three legs, two separate and distinct uteri with appendages may be found in the pelvis. A few cases are on record where there is complete fusion throughout, with exception of the Müllerian tract, which fails to fuse. Thus two uteri are formed, each with two tubes and two ovaries. These cases which are exceedingly rare, are in reality twins who have undergone complete fusion with the exception of the Müllerian tract.

A small accessory uterus was found by Skene in front of a well-developed uterus. The same finding was made in another instance by Hollander, and again by Olliver.

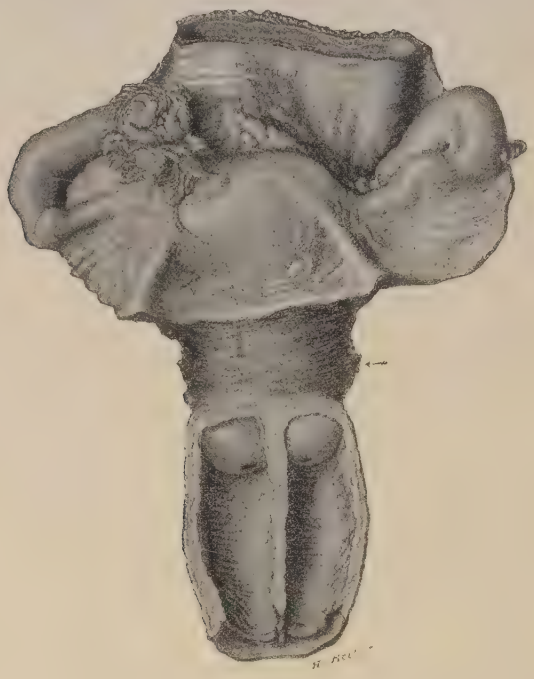

FIG. 214.—Uterus biseptus, with vagina duplex. Tuberculosis of both tubes and the peritoneum. (Kelly and Noble, case of Dr. G. Y. Rusk, N. Y.)

A trifid uterus is described by DePage in the case of an unmarried girl, in which there was a bicornuate uterus with a single cervix and a third uterine lobe attached to the cervix and filled with blood. As in the other cases, this condition was discovered accidentally in an abdominal section.

Congenital Prolapse of the Uterus.—Prolapse of the uterus in the newborn, in infancy, or in childhood is a rare occurrence as compared with prolapsus uteri in multiparæ. Nevertheless, it occurs with sufficient frequency to justify the presentation of the subject in a work of this nature. Weinberg estimates the frequency of prolapse of the uterus in the newborn and in nulliparous women at 3.34 per

cent. of all cases of prolapsus uteri, while Scanzoni would place the percentage of frequency at 13.15. In the absence of childbearing it is observed that prolapsus uteri is more often found in the newborn than in older children. In the case reported by Schaeffer the uterus and vaginal walls were found completely prolapsed in the second half of intra-uterine life. In this instance, as in so many others, a spina bifida accompanied the prolapsus.

The association of spina bifida with prolapsus has been observed in such a large proportion of cases that many authors have arrived at

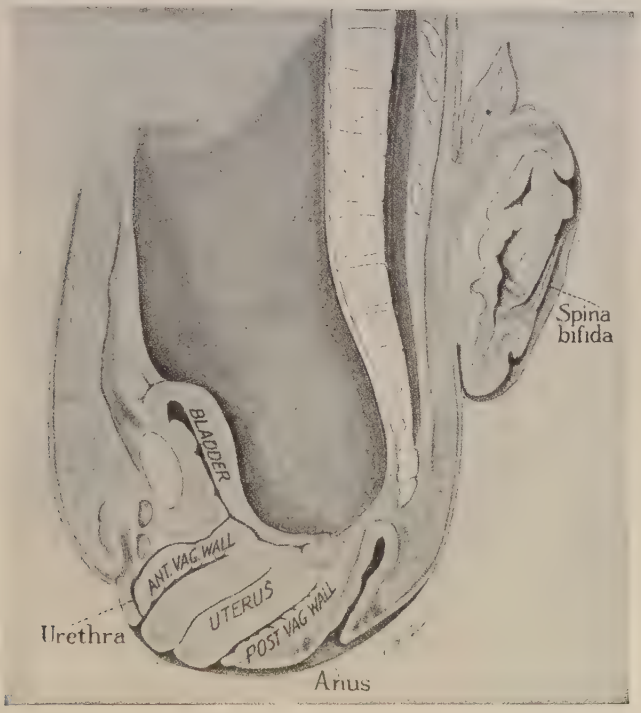

FIG. 215.—Case of congenital prolapsus uteri with spina bifida. The uterus lies below the level of the pelvic outlet and is retroverted. (Ballantyne and Thomson.)

the conclusion that there exists a causal connection. Approximately 86 per cent. of all cases of prolapsus uteri in the newborn are associated with spina bifida in the lumbosacral region, and if we were to include all cases in which a spina bifida occulta exists, the percentage would be much greater. In this connection we note the observations of Ebeler, who rayed 28 multiparous women without prolapse of the uterus in which but three revealed a spina bifida occulta. He then checked up with 28 multiparæ with prolapse of the uterus and found a spina bifida occulta in 23 of this number. These observations are very suggestive of a causal relationship. It is further argued by Ebeler that

neural disturbances with secondary muscular insufficiency of the pelvic floor is an important factor in the development of prolapsus uteri.

Krause asserts that the resultant cord lesion in spina bifida accounts for faulty innervation of the pelvic supporting structures. Ertzbischoff restricts the enervating influences to the uterine ligaments alone; while Halban and Bruger believe that only the muscles of the pelvic floor are affected. Heil would include the pelvic fat, connective tissue, fascia, muscles, and ligaments which he finds to be atrophied, ascribing the condition to faulty innervation.

Inasmuch as the greater number of cases of spina bifida are not associated with prolapse of the uterus, we must look to other contributing causes. We find in the records of these cases that prolonged and excessive physical exertion is an important factor. As a rule, the prolapsus is not in evidence at the time of birth but usually becomes manifest in the early days of life. Where occurring about the time of puberty or even later in the life of the Nullipara, we note that prolonged physical exertion, as the result of heavy lifting, chronic cough, and constipation are immediate exciting factors. Malnutrition is another factor to be reckoned with, as in several cases reported where young girls were poorly nourished and had tuberculosis of the lungs, and an accompanying persistent cough.

Munroe, in 1735, reported a case of procidentia in a girl three years of age. A larger number have occurred about the age of puberty. In all of these cases malnutrition was doubtless an important factor. Other factors have been suggested, such as visceroptosis, congenital widening of the hiatus genitalis, congenital deepening of the recto-vaginal pouch, and oversized pelvis.

Numerous congenital defects are found associated with prolapse of the uterus in the newborn. Aside from spina bifida, there have been recorded the following lesions: Hydrocephalus, ankle clonus, club feet, scoliosis, kyphosis, flat or perpendicular pelvis, infantile uterus, flat and shallow vagina, elongated cervix, prolapse of the rectum, inguinal hernia, paresis of perineal muscles, and disturbed sensation in the lower extremities. It is highly probable that an element of infantilism is in evidence in all these cases.

The relation of mental defects to prolapsus uteri in the newborn is suggested by the observations of Keplar who collected 80 cases of procidentia in nulliparæ, of which number 38 were mentally defective and included idiots, cretins, and imbeciles.

The management of these cases in the newborn and in infancy and early childhood should be conservative, reserving all operative procedures to a later time. The uterus may be replaced and held in position by vaginal packs of gauze or lamb's wool. Not until puberty, however, should operative interference be considered. As a matter of fact, few of these cases live to maturity. Death is not the result of the prolapsus but rather of associated lesions.

Malformations of the Vagina.—We have learned that the vagina is the result of canalization and fusion of the lower ends of the ducts of

Müller. As a result of faulty fusion and canalization, we are confronted with various anomalies in development, notably absence, atresia, and septate vaginæ.

Absence of the Vagina.—No trace of a vagina may be found in teratologic conditions, such as sympodia. In otherwise well-formed individuals complete absence of the vagina probably does not exist. In such cases as have been reported, it is probable that on careful dissection some fibromuscular tissue may be found between the rectum and bladder.

Atresia of the Vagina.—All gradations of atresia may exist in the vagina. It may be represented by a fibromuscular cord. There may be a very narrow lumen extending part way or throughout its length; or a membranous septum may be found at any point within an otherwise patent vagina.

Associated with an atresic vagina are malformations of the external and internal genital organs. Where the uterus and ovaries are fully developed, an atresic vagina will become manifest after the onset of puberty, when the menstrual blood accumulates above the point of obstruction and forms a blood mass within the upper segment of the vagina (hematocolpos), the uterus (hematometra), the tubes (hematosalpinx), or the pelvis (hematoma). Such accumulations of blood increase in size with each menstrual flux and eventually call for relief from pressure symptoms. Where both vagina and ovaries are absent, doubt may arise as to the sex of the child.

An imperforate vagina is seldom recognized before puberty and sometimes not until marriage. It has happened in childhood that the vagina has distended with mucus and so pressed upon the bladder and rectum as to produce dysuria and constipation.

There is no occasion for interference before puberty. If the menstrual flow is not obstructed or is absent, there is no need of surgical intervention save in preparation for marriage. For a detailed description of the management of these cases after puberty, see standard textbooks on Gynecology.

Double or Septate Vagina.—With failure of fusion of the lower ends of the Müllerian ducts, there is developed a septum which divides the vagina into two lateral halves; rarely does a septum divide the vagina into an anterior or posterior compartment. This septum varies in thickness. It may be deficient above or below; or it may be represented merely by a ridge. This condition, strictly speaking, is not a double vagina but rather a single vagina divided into two more or less symmetrical compartments. It is commonly associated with a septate uterus. Where the uterus is double, as is occasionally the case, a cervix opens into either half of the vagina.

One or both halves of the vagina may be imperforate. When such a condition exists, the menstrual blood may accumulate above the atresic point as in the case of an atresic vagina where the uterus and ovaries are fully formed. Ordinarily no disturbance is created by the presence of a vaginal septum unless it offers obstruction to the passage

of the child in labor. The condition will not be recognized in childhood and demands no consideration at this time. Later, operative procedures may be considered.

Malformations of the Hymen.—The hymen is generally believed to be a remnant of the cloacal appendage. It is an elastic mucous fold separating the vagina from the vulva. It is composed of fibrous and elastic tissue covered with flat epithelium and is well supplied with capillaries and nerves. Great variations in form and structure are observed.

Imperforate Hymen.—Where the hymen presents no openings for drainage, mucous secretions are retained within the vagina and are known to cause disturbance in childhood. Ordinarily, however, an imperforate hymen will occasion no inconvenience before puberty,

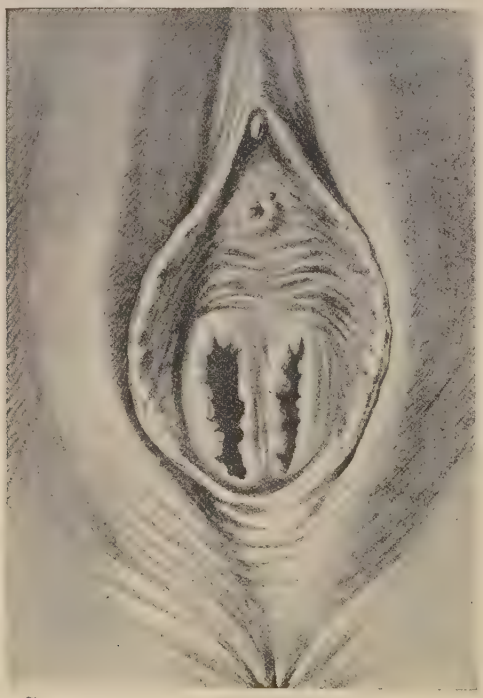

FIG. 216.—Case of double vagina. (After Barozzi and Fournier.)

at which time there is a blocking of the menstrual blood above the hymenial diaphragm, leading to conditions similar to that noted in atresia of the vagina. Indeed it is quite probable that many cases of so-called imperforate hymen are in reality cases of the latter malformation. There will be no occasion for surgical interference before puberty. In fact the condition is seldom recognized until the pent up menstrual blood produces symptoms which call for investigation.

Adhesion of the labia minora has been mistaken for imperforate hymen, and it is only when the labia are separated that the hymen is inspected.

Double Hymen.—Two membranous diaphragms may be formed, one lying above the other. Such cases are to be regarded as atresia of the vagina, reserving the actual condition of double hymen for the rare instances where there is a double vagina.

Absence of the Hymen.—Entire absence of the hymen probably exists in monstrosities and never in well-developed individuals. Folds of mucous membrane, however obscure, are to be found in all cases.

A great variety of forms exist, notably where there are several openings (*hymen cribiformis*), where the hymen is circular or crescentric, where it is bulging (infundibuliform), and where two large openings divide it into two unequal halves (*hymen septus*).

Great variation exists in the thickness, vascularity, and resistance of the hymen. Instances are known where even childbearing has failed to rupture it.

Malformations of the Vulva.—The vulva may present defects in development, even in the presence of well-formed internal genitals, though the combination of anomalies is sufficiently frequent as to suggest the presence of malformations in the internal genital organs whenever defects in development are observed in the vulvar structures.

Defectus Vulvæ.—Absence of all vulvar structures, in which there is a smooth cutaneous surface passing from the pubis to the coccyx, is an anomaly which is found only in monstrosities. In rare instances an oval orifice is observed, but no vulvar cleavage is in evidence. Above the genital ducts, rectum and bladder open into a single cavity (persistence of the urogenital sinus). The abdomen of the fetus may be distended by accumulated urine in the cloacal sinus.

Atresia Vulvæ.—An apparent absence of the vulvar cleft may be caused by adhesions of the labia majora and minora in fetal life. The occlusion may be complete, but in nearly all instances an opening is found near the clitoris which provides for the escape of mucous secretions, urine, and menstrual blood.

The cause of the atresia is doubtless an adhesive vulvitis occurring either in fetal life or in infancy. Little difficulty will usually be experienced in separating the labia by the fingers. Failing in this, they may be separated by the knife, using a sound through the small opening near the clitoris as a guide.

Vulva Infantalis.—The infantile type of vulva may persist throughout childhood and adult life. Infantile characteristics are usually observed in the internal genital organs as associated lesions. Chlorosis is a common accompaniment.

Double Vulva.—Two separate and perfectly formed vulvæ have been reported by Katharine Kaufmann and Chiarleoni. The condition is so rare, however, as to merit no extended comment. Gemmell and Paterson reported a case of double vulva in a mature woman in which a child was born through each vulvar aperture.

Atresia Ani Vaginalis.—The opening of the anus into the vagina as a congenital lesion is due to a *persistent cloaca*. The normal anal

opening does not exist, so that the anus communicates either with the vulva or vagina. This defect is due to the absence of the lower end of the Müllerian duct, which under normal conditions forms the lower segment of the vagina. In the majority of cases the anal opening is immediately behind the hymen, though it may be above or below it.

The feces are passed through an opening near the vestibule or posterior commissure. Where no sphincter exists there is no control over the feces.

The management of these cases throughout infancy and early childhood consists in keeping the parts as clean as possible. After 15 or 16 years of age, operative interference is advised if no sphincter action is present. If, however, the bowels are controlled by a sphincter, operation may or may not be advised.

Hypospadias in the Female.—It may be contended that the normal woman is a hypospadiac man. There are, however, a few cases on record of so-called hypospadias in women in which the urethra opens into the vagina, in which, in reality, there is a persistence of the urogenital sinus. In these cases the vagina, the sinus urogenitalis, the anus, and perineum are well formed. The urine, mucous secretions, and menstrual blood pass through a common opening at the base of the clitoris, which is enlarged in most cases and suggests the male type. Again we find in rare instances an absence of the urethra, with the vagina and bladder opening into the vestibular canal. This condition gives the bladder the appearance of opening directly into the vagina. In these cases the allantois at its lowest segment was incorporated into the bladder rather than in the formation of a urethra. The chief symptom is incontinence of urine.

Epispadias in the Female.—Strictly speaking, the term epispadias applies to cases in which the upper wall of the urethra is defective. It is not an infrequent occurrence to find exaggerated conditions in which the defect involves both the bladder and abdominal wall, and in which there is an open groove passing underneath the symphysis pubis to the bladder. The entire length of the urethra or only a segment of it may present this cleavage. The clitoris is bisected, the two halves lying on either side of the urethral groove. The symphysis pubis may be united or separated. The bladder, which rarely possesses its normal capacity, may be extroverted together with divergent labia majora. Instead of the bladder, the cloaca may present, no separate bladder having developed. Incontinence of urine is the predominating complaint. This incontinence may not be complete, but is always sufficient to cause great distress and annoyance. Excoriation of the skin of the thighs and infection of the urinary tract, both of which are the result of incontinence, are occasional complications.

No attempt should be made to remedy the condition in infancy. Later, when puberty is reached, the parts should be freshened and the edges brought together. Where the gap is too great for such repair, a urinal should be adjusted.

Malformations of the Clitoris and Labia.—A bifid or split clitoris is an occasional finding. It is rare that this condition presents itself as a solitary anomaly. Usually it is associated with epispadias and ectopia vesicæ. Hypertrophy of the clitoris, both congenital and acquired, is a rare anomaly, and when associated with adherent labia, it presents a condition in which the external genitals are highly suggestive of the masculine type.

Hypertrophy of the labia minora is best exemplified in the "Hottentot apron," which may be said to be a racial characteristic.

Hermaphroditism.—Under the term hermaphroditism we will include both those cases in which the organs of both sexes are represented and those cases in which the sex is doubtful. In the early state of the development of the embryo, it is not possible to determine the sex. The sexual gland has not become differentiated into an ovary or testicle; the genital tubercle has not developed a clitoris or penis; and the Müllerian and Wolffian ducts have not yet declared their intention as regards further development. This early state is one of sexual indifference. Before development can proceed further, some morbid and as yet unknown process may disturb the normal scheme of growth, so that the individual may remain sexually indifferent. An ovary and testicle may develop side by side, or a uterus may be associated with a well-formed penis. No case has yet been reported where an ovary and testicle are found on the same side, but cases are not rare in which the Müllerian and Wolffian ducts atrophy or hypertrophy simultaneously, so that the external genitals present such complex developmental anomalies as to suggest a combination of both sexes.

In this discussion the classification of Klebz will be adopted. This classification includes the true and false types of hermaphrodites.

True Hermaphroditism.—According to the classification of Klebz, true hermaphroditism may be bilateral, unilateral, and lateral. In the bilateral hermaphroditism an ovary and testicle are found on either side, while in unilateral hermaphroditism there is an ovary and testicle on one side and either an ovary or testicle on the other, or an absence of both on one side. No authentic case in the human has been found of either. Ballantyne questions the existence of the lateral type, *i.e.*, where a testicle is found on one side and an ovary on the other. He rightly contends that no case can be accepted as an example of true hermaphroditism without a thorough post-mortem dissection. The conclusion he reaches is that true hermaphroditism does not exist.

Pseudohermaphroditism.—There is, however, no scarcity of case reports on pseudohermaphroditism. This is a condition in which there are anomalous developments of the external genitals, not infrequently leading to confusion in the determination of the sex. Such confusion prevails particularly during the period of infancy. Where ovaries exist, the individual is a female, no matter what the external genitals may reveal; where testicles exist, the individual is a male, even though the external genitals have the appearance of vulvar structures. In distinguishing these characteristics, therefore, we have adopted the

nomenclature of pseudohermaphritism feminimus and pseudohermaphroditism masculinus. The sex peculiarities may be found in the internal genital organs, the external genital organs, or in both combined. All manner of combinations are possible; the individual may possess testicles and the external genitals of the male and nevertheless have a uterus, tubes, and vagina. On the other hand, the testicles may identify the individual as a male, while the external genitals are those of a female with the uterus and vagina intact. The ovaries may be well formed, but the external genitals are those of the male, with the Wolffian duct displaying some degree of development. Great confusion was occasioned in a single instance where the ovaries were found in the inguinal canal, and where, at the same time, there were external genitals of the male, and a growth of hair on the face. In scrotal hypospadias, with an infantile penis which may be imperforate and fixed by adhesions under symphysis pubis, the suggestion of the female type is strong. Confusion is still further enhanced by the presence of atrophied undescended testicles and enlarged and even secreting breasts, together with absence of hair on the face.

Errors in the determination of the sex may not be corrected until the age of puberty and in many instances not until marriage. Indeed, there are instances on record of the male type not being disclosed even by marriage. In the female, failure to establish the menstrual functions will usually lead to a disclosure of the real state of affairs. Such individuals are usually sterile, due in part to the under-development of the sex glands, and in part to the malformed external genitals. The general sex characteristics of the individual may in some cases be so altered from the normal as to lead to great confusion. For example, the masculine type of hermaphroditism may present secondary sex characteristics of the female, such as broad pelvis, small larynx, enlarged breasts, female distribution of the hair, and general rounded outlines. Hemorrhages simulating the menstrual flux are known to have occurred as a result of *coitus per urethram.* In these cases there is mental and moral perversion. Degeneracy is a not uncommon accompaniment of this sex perversion. On the basis of greater frequency of masculine hermaphrodities, Lawson Tait has advised that all such should be brought up as boys, when doubt exists as to their real sex, because the chances are 10 to 1 in favor of a male sex-ensemble.

It may be seriously questioned if surgery has a place in the management of these cases. Where the external genitals are those of the female, the testicles have been removed with the apparent development of female secondary sex characteristics. Such a procedure, however, appears to the author as highly speculative and unjustified.

Vulvitis.—Vulvitis in children is a not uncommon occurrence. In point of frequency we have first to consider inflammations of the vulva resulting from uncleanliness. Such cases are not infrequent among the ignorant and poor classes. The remedy is to be found in simple cleanliness in the care of the child. In addition to bathing and the use of clean napkins, the irritated surface should be kept well

powdered with talcum. Relief will then be speedily obtained. Scratching or irritation from pediculi and oxyurides may result in a distressing inflammation of the vulvar surface and can only be remedied by the removal of the exciting cause, together with the exercise of cleanliness and the application of soothing ointments, lotions, and powders. In all cases of vulvitis, gonorrhea is to be suspected, but no indication of such a suspicion should be conveyed to the mother, unless the gonococcus has been demonstrated in the secretions. Where recent rape is suspected, the parts are to be carefully inspected for contusions and lacerations. No conclusion in such a case is justified without first making a careful search for spermatozoa in the vaginal secretions.

In the acute stage of vulvitis the parts are red and swollen, and this redness may spread to the inner surface of the thighs. The parts are very tender. Upon separating the labia a purulent secretion exudes. It is again emphasized that all such secretions are to be subjected to a searching microscopic examination. This procedure is of considerable importance, because of possible legal complications and because of the choice of therapeutic measures to be employed in event of finding the gonococcus. The subject of gonorrheal infection is treated in its entirety in a separate chapter.

Ulcerative vulvitis is a term synonymous with aphthous vulvitis. Children between the ages of two and five who have recently passed through an exanthematous disease occasionally develop circumscribed spots upon the vulvar surface. These spots sometimes ulcerate and may become gangrenous. When gangrene develops, the lesion is readily confused with that fatal malady known as noma pudendi. In ulcerative vulvitis, the gangrene is an accidental sequela, while in noma pudendi the gangrene is an essential characteristic.

In the management of these cases everything possible should be done to improve the general condition of the child. The affected parts should be kept as clean as possible by frequent baths and external antiseptic douches. Lysol in the proportion of ½ dr. to 2 qt. of warm sterile water is an effective douche. The vulva should be covered with a compress of surgical gauze or sterile absorbent cotton dampened with the following solution:

Formalin	Miv
Glycerin	℥iv
Sterile water	oi

From time to time, the ulcers should be painted with the tincture of iodin or with a 10 per cent. solution of the nitrate of silver.

Noma pudendi is a specific form of gangrene of the vulva found in young children. The disease is almost invariably fatal. Should the patient chance to survive, the resultant scar tissue causes more or less deformity of the vulvar structures.

Exanthematous diseases are the usual forerunners of the lesion, just as is the case with noma of the face. At the onset there is burning

pain and fever. The vulvar tissues become edematous and discolored, assuming a dark-red, gray, brown, or black appearance. Bullæ form, and with the rupture of the bullæ, an ichorous serum is discharged, leaving a dark slough. Supportive treatment is most essential. All possible efforts should be directed toward increasing the resistance of the individual. External douches and antiseptic moist dressings are applied as in the case of ulcerative vulvitis (*vide supra*). The gangrenous areas should be treated by the actual cautery or the affected parts widely excised.

Erysipelas vulvæ occurs in neglected young children. The reddened edematous surface, together with a burning sensation and fever, is as characteristic of erysipelas of the vulva as in other parts of the body. The author recalls a case of erysipelas vulvæ in an infant which traveled throughout the genital tract and resulted in a general peritonitis.

It is questionable if any form of treatment will effectively check or abort the disease. The surface should be dusted with boric acid powder or salicylic acid and from time to time painted with nitrate of silver. Compresses of carbolic acid or corrosive sublimate solution in very weak dilution should be continuously applied. General supportive treatment is essential.

Pruritis Vulvæ.—Itching of the vulva in children is usually the result of uncleanliness. The influence of soiled napkins, for instance, leads to irritation of the vulvar surface, and this in turn to itching. On the other hand, there are irritating discharges from the vulva and vagina in infants and young girls which may also produce itching, usually of the most distressing character. Such discharges are not uncommonly gonorrheal in origin. Glycosuria and intestinal parasites must also be considered as causes of pruritis vulvæ. In all cases the urine must be examined for sugar. Thread worms, scabes, and pediculi are to be sought for. Finally, eczema is known to be both the cause and effect of pruritis vulvæ. Where a definite cause is found, it must, if possible, be relieved. Glycosuria is to be treated by proper dietary and medicinal means. Irritating discharges are to be treated by frequent baths and vaginal and vulvar douches of a mild antiseptic solution, notably lysol in the proportion of ½ dr. to 2 qt. of warm water. The vaginal douche may best be given through a catheter introduced through the opening in the hymen. The vulvar surface may be bathed with a solution of borax (4 dr. to 1 qt.) and lig. potassæ (2 dr. to 1 qt.). In addition to such alkaline solutions, resort may be had to ointments and lotions, such as lotio plumbi, lotio calaminæ, and zinc ointment. A 10 per cent. icthyol ointment will sometimes give the desired relief, as will resinol ointment. Menthol, 2 per cent. in almond oil, may be tried. Chlorotone combined with adrenalin, as an ointment, has been found effective in some cases. Zymocide as a lotion, in the proportion of 1 to 5 parts of water, has been extolled. No single remedy will give results in all cases, and all remedies may fail. All that can be done is to try one remedy after

another in the hope of obtaining relief. When all remedies have failed, the judicious application of the *x*-ray, radium, or the high frequency current may be resorted to, but in children they are to be used with the greatest caution for fear of burns. I can conceive of no case in childhood so obstinate and distressing as to justify the excision of the affected parts.

Disorders of the Menstrual Functions and Sex Characteristics.—Perfect womanhood is not obtained without the development of sex characteristics. These characteristics are in nature both physical, and psychical and embrace menstruation, conception, parturition, and lactation. In dealing with the subject of diseases of childhood, it will not be out of place to discuss the subject of disorders of puberty and the derangements of sex characteristics, and in doing so, reference will be made to the physiology of the female sex organs, because much is learned of the disordered functions of the reproductive organs by recent developments in physiology.

Sexual maturity in the human female is marked by the onset of menstruation. It is at this time that the general metabolism shows marked alterations and the mental status is changed. Physical changes are marked by the growth of hair in the axilla and on the mons veneris and labia. The body in general becomes rounded out. The breasts enlarge and the labia become more prominent. It is at this time that the uterus shows marked enlargement, the growth being particularly manifest in the body as compared with the cervix. The ovaries become broader, and ripened follicles develop. Corpora lutea now appear at intervals, and interstitial glands develop within the substance of the ovary.

In addition to the changes in the ovaries and mammary glands, it is of interest to note that the parotid and thyroid glands increase in size, a fact which has led to interesting speculations on the relation of certain ductless glands to the menstrual functions.

Influence of Ovarian Secretion upon Development.—The ripening of the follicles and the appearance of corpora lutea in the ovary are synchronous with the appearance of menstruation and the phychical and physical changes which mark the onset of puberty and the development of sex characteristics. It has been generally accepted that an ovarian secretion is created at this time which persists throughout the period of sexual maturity. With the appearance of the menopause, and with the accompanying atrophy of the ovaries, this secretion disappears. As a result, the sex organs cease to function, and there are marked alterations in the general metabolism and in the psychical characteristics of the individual. Where both ovaries have been removed in childhood, menstruation and its accompanying phenomena are held in abeyance. Where the ovaries are removed shortly after the establishment of puberty, menstruation will cease, but growth and nutrition of the individual do not suffer radical changes.

The metabolic changes which occur as a result of the removal of both ovaries in early girlhood are not well understood. It appears

that ossification of the long bones is delayed, so that they become unusually long. There is a marked tendency to a deposit of fat throughout the body. It is affirmed by many and denied by some that the calcium output is diminished. More than this we cannot say.

The whole endocrinous system is so finely adjusted that the increase or decrease in the secretion of one ductless gland may upset the balance in the whole system. The harmony or disharmony of the reproductive functions is closely related to the secretion of the ductless glands. This much we know; but the literature which has developed in the last decade upon this subject leaves us in a hopeless state of confusion. So vague and intangible is the whole discussion that it would serve no good purpose to attempt to formulate any conclusions. All that we can now say is that we are not in a position to ascribe to any particular organ the sole function of regulating any given physiologic function. The whole endocrinous system must be taken into consideration, but in what manner and to what extent we are at present in no position to assert. If we eliminate the ovaries, we cannot say that the disorders incident to the procedure are due solely to the absence of the ovarian secretion. It may be that these disordered functions are chargeable to excessive secretions on the part of some other ductless gland which has been deprived of its control. We believe we know that the organs essential to the functions of the reproductive organs are the ovary, thyroid, adrenals, hypophysis, parathyroids, thymus, and pineal gland, but the dual function of these organs and their interrelation one with the other remains largely an unsolved problem.

Absence of Puberty.—Puberty may never be established. The explanation lies in some local or general disorder. The organs essential to menstruation may never have developed or may be wholly wanting. The best example of this lack of development is found in cretins, in whom the fault lies with the endocritic system. It is possible that in such individuals the menstrual functions might be preserved by timely treatment in early infancy. It has been observed that cortical neoplasms in the suprarenals has resulted in atrophy of the sexual organs. General infantilism finds expression in an absence of sexual development. Blair Bell suggests that certain hormones arising from the endocritic system are suppressed or lacking and thereby fail to stimulate normal growth and development. He cites Byron Bramwell who finds that some of these cases are due to pancreatic infantilism.

In all such cases there is little encouragement in treatment.

Delayed Puberty.—The advent of puberty as expressed by the first appearance of menstruation varies within wide limits. In the experience of the author the usual time of onset is 13 to 14 years of age. In rare instances puberty is established as early as 11 years and as late as 21 years. We may say that puberty is delayed when menstruation, the development of the sex organs, and sex characteristics in general do not appear prior to the seventeenth year. Beyond this limit, we cannot regard the condition as normal.

It is not to be understood that menstruation alone marks the advent of puberty. Menstruation is but an expression of matured sex organs; hence it follows that the development of these organs, notably the uterus and ovaries, must precede the appearance of the menstrual flux. In fact, these structural developments are essential to the rounding out of that epoch in the life of young girls which we call puberty. More than this, the sex characteristics of adult life make their appearance at this time if puberty is to be established on a perfectly normal basis.

The term "*incomplete puberty*" has been applied to cases in which the sex organs and sex characteristics have developed, but in whom there is an absence of menstruation. Such a condition may be temporary or permanent; temporary when due to constitutional disturbances such as malnutrition, anemia, and altered internal secretions, or to malformations and under-development of the sex organs. Hypoplasia of the uterus and ovaries, the existence of an atresic vagina, or septum of the vagina are tangible factors in forestalling the menses.

There are unquestioned psychical causes for delayed puberty. Just what part is played by the endocritic glands is not definitely known, but that they are important factors cannot be questioned. Unhygienic conditions, overwork, both physical and mental, are factors which must be reckoned with, for it is a matter of common observation that girls between the ages of 12 and 20 who are denied the conditions essential to a healthy normal life, who are overworked in shop and in schoolroom, very commonly menstruate late in life. In fact, if these conditions prevail, they seldom develop normal sexual functions. As a result of faulty environment and over-exertion, both physical and mental, they are destined to menstruate perhaps scantily and usually with much pain and irregularity. Normal habits of life in the developmental years of a girl's life begets normal sexual functions.

Change of environment is a factor in delayed puberty, as is also change in occupation. It is a matter of common observation that girls who go far from home to attend school or to engage in some occupation do not establish their menstrual functions at an early date. If puberty has been established before making so radical a change in environment and habits of life, there is much likelihood of a cessation of the menstrual periods for several months and even for a year or two. Mothers need not be concerned about their daughters under such conditions. As soon as they are fully adjusted to the changed conditions, the menstrual functions will become reestablished and without medication.

Precocious Puberty.—The menstrual blood has been known to make its appearance as early as the second year of life. Numerous cases are on record where puberty has been established between five and nine years of age. Such cases, which are examples of precocious development, are not normal. It may happen in infancy that blood appears on the napkins; whereupon the mother may interpret such ar

occurrence as a menstrual flux. Frequently, however, such a blood flow is a deposit of urates; or it may be chargeable to excoriations of the vulva from infection or from irritation due to soiled linens. In rare instances, tumor growths, notably sarcoma of the cervix, are responsible for the loss of blood. In exceptional cases the cause of the bleeding cannot be discovered. It is not to be inferred under any circumstances, however, that the loss of blood is truly menstrual unless the sex organs are fully developed. Precocious menstruation must go hand in hand with precocious development of organs essential to menstruation. Ovarian tumors and hyperplasias are said to develop prematurely the sex organs and sex characteristics. Masculinity is not feminine precocity; it follows then that tumors and hyperplasias of the suprarenal cortices and pineal gland which produce precocious puberty in boys can no more than conduce to masculinity in girls. Roger Williams recorded 11 cases of precocious puberty in girls in all of which ovarian tumors were found. In this series, eight were sarcomata, two were benign cysts, and one a fibroma. On the other hand, Gautier reported 23 cases of sarcomata of the ovary in childhood, only four of which were examples of precocious puberty. Heredity, masturbation, environment, and disordered functions of the endocritic organs are contributing factors in cases of early puberty, *i.e.*, puberty commencing between the ages of 9 and 11.

In all cases of precocious development, it is imperative that the child should be closely guarded lest she be led into sexual excesses and develop sexual neuroses.

Tumors of the Uterus, Ovaries and Vagina in Children.—Tumors of the female genital tract of children are not common, but of late years cases of such disorders have been recorded with increasing frequency. Inasmuch as a large proportion of these tumors are malignant and are usually not recognized until far advanced, the subject is one of very grave importance. Almost all tumors of the uterus and vagina of childhood are malignant, whereas in the ovary we find a fair proportion of benign cystic and dermoid growths, which may develop slowly and escape recognition until adult life. On the other hand, malignant tumors of the pelvic organs develop with extreme rapidity in infancy and childhood, although the general health may not be noticeably influenced until the disease has become far advanced.

In discussing the development of genital tumors, Brüning and Schwalbe refer to mechanical disturbances of the circulation as a causal factor. Askanazy calls attention to certain remarkable appearances associated with certain classes of tumors and finds one etiologic factor to be hypersecretion of the ductless glands.

Benign Tumors of the Uterus in Childhood.—Benign tumors of the infant uterus probably do not exist. The earliest reported case of a uterine fibroid was that of Cavillon. In this instance the child was 13 years of age. Nuernberg found myomata in the uterus of a young child and inferred that they were embryonic in origin.

Malignant Tumors of the Uterus in Childhood.—With few exceptions malignant tumors of the uterus in infancy and childhood are sarcomatous. Several cases of cancer of the cervix are recorded from reliable sources. Steffins records five malignant tumors of the infant uterus, of which three were sarcomas and two carcinomas. He believed that inasmuch as all were recognized between the ages of five months and two years, that they were all congenital. He also has reported three cases of combined malignant tumors of the uterus and vagina. The author examined the gross and histologic specimens of an adenocarcinoma of the cervix removed from an infant of six

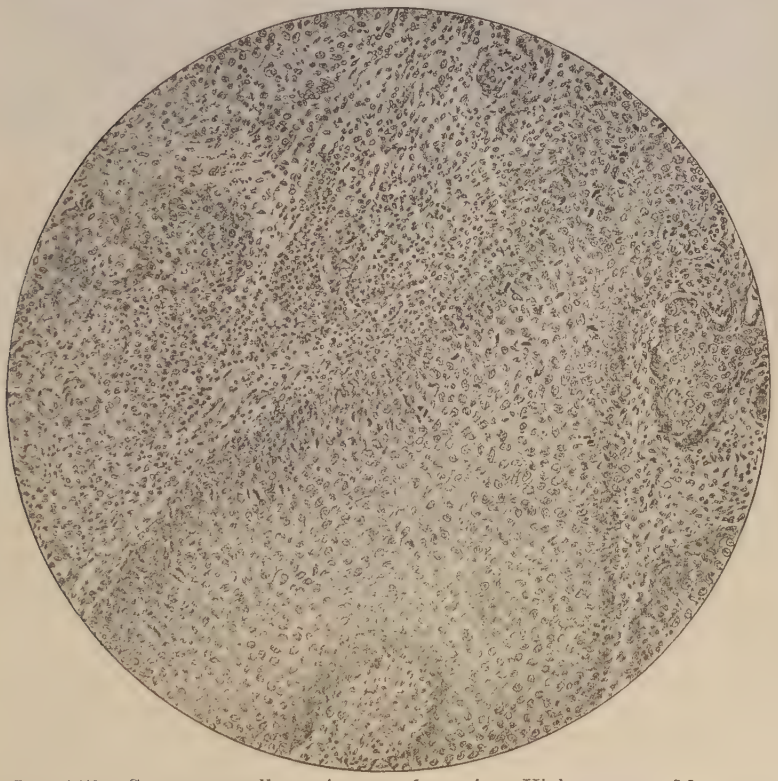

FIG. 217.—Squamous-cell carcinoma of cervix. High power. Most of the tissue consists of large epithelial cells which vary greatly in size, and are infiltrated with a few round cells. A few strands of stroma are seen thickly infiltrated with round cells. Between these two tissues there is no basement-membrane, and the typical basal layer of cells found in stratified squamous epithelium is missing. (Graves "Gynecology.")

months by Professor Franz in the Charite' Franenklinik of Berlin. In this case a complete hysterectomy was performed, the child living 10 days after operation.

Some years ago, the author observed a case in which a child of 18 months had a nodular pelvic tumor weighing 4 lb. This abdominal growth was preceded by a sarcoma botryoides of the cervix which

had been previously removed. The abdominal growth was a round-cell sarcoma.

Rosenstein's case of carcinosarcoma of the uterus, aged two years, died 14 days after operation.* Ganghofer's case, aged eight years, with a uterus 2.6 cm. long, containing a cancerous tumor of the size of a crown piece, died from an intercurrent variola.† Blum's case, aged 11 years with sarcoma of the uterus, died from recurrence.‡ Bluhin's case of sarcoma botryoides cervices in an 11 year old girl recovered.§ Bradford's case, a girl of nine years with papillary cystoma, the size of a head of a full-term fetus, was well three months after a complete hysterectomy.‖ Odebrecht's case with sarcomatous degeneration of a uterine myoma recovered after operation.¶ Worrall's case of adenoma of uterus and double ovarian tumor recovered completely.** Little's case of carcinoma of uterus in a 14 year old girl was fatal.†† The case of Adams is most unusual in that an advanced cancer of the cervix and body of the uterus was found in a child of two and a half years of age.

Tumors of the Ovary in Childhood.—The frequency with which tumors of the ovary are found in infancy and childhood, as compared with similar growths in the uterus and vagina, is most striking.

In 1513 tumors of the ovary collected by Olshausen, 61 occurred in children under 10 years of age. Doran found a sarcoma of the ovary in a living seven months premature child. The greatest number occur in childhood between the ages of 10 and 14 years. When occurring in the late years of childhood, evidences of precocious sexual development have occasionally been observed. Hair appears on the pudenda, the breasts enlarge, and the menses may make their appearance, together with the development of general sex characteristics. Upon removal of the tumor the menses lessened in amount but continued to recur with more or less regularity.

Jochmann, in 1898, recorded 20 cases of solid tumors in children. Hubert, in 1901, recorded 175 cases of both cystic and solid tumors up to the age of 17 years, as follows:

Benign tumors:	
Dermoids	39
Cystomata	19
Cysts	53
Haematomata	4
Malignant tumors:	
Carcinomata and cystocarcinomata	28
Endotheliomata	4
Sarcomata and cystosarcomata	28

* Arch. f. Path. Anat. (1883).
† Ztsch. f. Heilk. Prag. (1888).
‡ Arch. f. Gyn., Bd. 68.
§ Med. Woch., iv, No. 175, p. 21.
‖ Arch. Ped. (1892).
¶ Zent. f. Gynaek. (1904), p. 2.
** Australasian Med. Gaz. (1893).
†† New Orleans Med. and Surg. Jour. (1896–97).

Klauhammer in his inaugural dissertation (Jena, 1912) states that approximately one-half of all ovarian tumors in childhood are dermoids. Hubert found 60 malignant tumors in 175 ovarian tumors in children, a proportion vastly greater than is found in adult life. Of the 60 malignant tumors, 32 were sarcomas and 28 carcinomas. The sarcomas were largely of the round-cell variety. Of the 1000 ovariotomies performed by Wells, only three were on children. In contrast we have the record of Olshausen, who performed 1716 ovariotomies, 61 of which were on children. Hubert records 202 cystic ovarian tumors in children, of which number 35 per cent. were cystomas, 31 per cent. dermoids, and 34 per cent. were malignant.

It is observed that cystomas increase in frequency as age advances. Doran reported proliferating cysts in the ovary of a seven months fetus; Boullard found numerous cysts in a still-born child; Lederer operated an infant of 15 weeks for cystic degeneration of the ovary; and Chiene removed an ovarian cyst in a child aged three months.

Numerous cases have been recorded in which sarcoma of the ovary has been operated between the ages of 2 and 18 years. Harris removed successfully a sarcoma of the ovary from an infant of 22 months, while two fatal cases are recorded by Hoffman and Cameron at 22 and 40 months of age. Byford had a successful case at the age of four years and eight months.

Rohrig removed a round-cell sarcoma of the ovary, the size of a man's head, from a 13 year old girl. The tumor was of rapid growth. There were no metastases and a moderate degree of ascites co-existed.

Guibal successfully removed an ovarian sarcoma from a child less than three years of age. The weight of the mass extirpated was 4.9 kg. and the child was said to be well 13 months after the operation.

Carcinoma of the ovary has been observed less frequently than sarcoma. Maryolin's case was less than one year old. Weil reports an adenocarcinoma of the left ovary in a child of five years which was the size of a large cocoanut and freely movable. Stolypinsky found a cancerous ovary in a girl of eight years, Leopold in a girl of nine years, Corse at 12 years, and Michel removed a cancerous ovary the size of a man's head in a child of 16 years. Michel's case died of recurrence two years later. It is of interest to note that ovarian tumors, even though malignant, are deceptive in that they rarely give rise to symptoms until far advanced. On numerous occasions they have only been recognized by an exploratory abdominal incision. When an abdominal tumor is observed in infancy or childhood, the diagnosis rests between dermoid cyst, sarcoma or carcinoma of the ovary, cystic or malignant disease of the kidney, or some unusual atypical renal disorder. Dermoid cysts existing in infancy may grow slowly and escape recognition until adult life. On the other hand, we find that benign proliferating cysts, sarcoma, and carcinoma of the ovary may attain large proportions in infancy. It is a noticeable fact that malig-

nant growths advance rapidly in childhood, though the general health is not early impaired.

Of all new growths of the ovary, sarcoma is the most frequent; this is particularly true of the congenital growths.

Inasmuch as malignant growths of the ovary usually escape recognition, the prognosis is most grave. Sutton collected 21 cases of sarcoma of the ovary operated in childhood with a mortality of 52.4 per cent. This record is in marked contrast to that in operations upon cysts, in which there is an 8 per cent. mortality.

Age is no contra-indication to operation. Whenever possible, ovarian tumors in infancy and childhood should be removed.

The author recently removed a multilocular serous cyst of the right ovary from a girl 15 years of age which weighed 24 lb. The patient made an uneventful recovery.

Kelly, Baginsky, and Henning find an advantage in operating upon children, while Bland-Sutton finds little encouragement in ovariotomies where the patient is very young. Sutton's views were largely colored by his disastrous experiences with sarcomas of the ovary in childhood. Kelly had a mortality of more than 50 per cent. in operations upon children under four years of age, but his results were more favorable as age advanced above four years.

Tumors of the Vagina in Children.—Primary tumors of the vagina are of rare occurrence in infancy and childhood. Benign tumors, notably cysts, fibroma, myoma, and fibromyoma, are extremely rare, while sarcoma and carcinoma are found with greater frequency. A few cases of chorioepithelioma of the vagina have been found in the years immediately preceding and following puberty.

It is a noteworthy fact that primary sarcoma of the vagina is more frequent in childhood than in adult life. In the series of 26 cases collected by Starfinger, 24 were in children under five years of age and 10 under one year of age. There are now about 40 cases on record. Sarcoma of the vagina may be congenital or appear early in infancy and childhood. The growth may arise from any of the connective tissues which are involved in the complicated developmental processes associated with the formation of the cloaca. Sarcoma of the vagina commonly assumes a polypoid form and may be single or multiple. Growth is slow, and ulceration is a prominent feature in advanced cases.

The prognosis of sarcoma is grave for the reason that the growth usually escapes recognition until far advanced. When removed early, recurrence is the rule. The general health of the child remains unimpaired until late in the course of the disease. Toxemia is a prominent clinical feature in advanced cases and is said in most instances to be the immediate cause of death.

Cancer of the vagina in childhood is extremely rare. Smith reported a case in an infant of 14 months; Guersant records a retrovaginal cancer in a child of 3½ years. Johannsky's case was that of a girl nine years of age with a cancer of the vagina the size of a hen's

egg. In the absence of microscopic reports these cases are open to the suspicion of being sarcomas. Ward's case is convincing, in that a microscopic examination identified an epithelioma of the vagina in a girl under 20 years of age.

Choreopithelioma of the vagina is reported by Schlagenhofer in a virgin of 13 years. Ahlfeld saw one at 17 years, and Champneys at 18 years.

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